THE DEVELOPMENT OF AN EPIDEMIOLOGICAL CASE DEFINTION FOR CHRONIC FATIGUE SYNDROME/MYALGIC ENCEPHALOMYELITIS (CFS/ME)

TOLU OSOBA

A thesis submitted in partial fulfilment of the requirements
of the University of the West of England, Bristol
for the degree of Doctor of Philosophy

*This research programme was carried out in collaboration
with the MRC-General Practice Research Framework
and the Action for ME.*

Faculty of Applied Sciences, University of the West of England, Bristol

19 August 2007

Abstract

Different case-definitions are currently employed in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME) epidemiological research. This makes it difficult or impossible to compare data across surveys or to assess epidemiological patterns across different time periods. Most of the current case-definitions for CFS/ME were designed for clinical research purposes. These are thus inappropriate for monitoring epidemiological indices of CFS/ME in the general population or for undertaking public health needs assessment in the UK. As a result, the Medical Research Council and Department of Health made recommendations in various reports for an epidemiological case-definition to be developed.

To develop the CFS/ME epidemiological case-definition, questionnaires were sent to GP members of the General Practice Research Framework in England, Scotland and Wales to identify patients with unexplained chronic fatigue of at least six months. The GPs were asked to fill in the questionnaires either from case-notes or during consultation. The survey featured questions based on the parameters of published case definitions of CFS/ME, demographic details and the GP's provisional diagnosis. The case-definitions considered were the CDC 1988 and 1994, the Australian, Oxford and Canadian consensus definitions.

An expert panel assigned cases to disease and non-disease group at four classification thresholds to allow assessment for their effect on sensitivity. Symptom patterns of 162 cases with unexplained chronic fatigue of at least six months were evaluated. The requirement for the exclusion of cases with a possible alternative explanation for the illness was also applied. The main discrimination techniques to identify significant variables for the case-definition included sum of binary variables and classical discriminant analysis.

Using the unweighted sum of binary variables, 14 variables accounted for significant variation in the data. Discriminant analysis showed that at the first three thresholds, three similar variables (a reduction in activity to less than 50% of the patient's premorbid activity, severe debilitating fatigue affecting physical and mental functioning, muscle discomfort) accounted for majority of the variation in the data. Further ROC curve analysis selected the best model [CFS- 97(67.4%); non-CFS- 47(32.6%)] which predicted 91.8% of CFS/ME cases correctly with a specificity of 69.8%. The analysis also revealed that the fourth threshold level comprised a smaller subset of patients [CFS-52 (36.1%); non-CFS 92 (63.9 %)] with an increased number and possibly a higher degree of severity of symptoms. The five key predictor variables at the fourth threshold level were- a reduction in activity to less than 50% of the patient's premorbid activity, myalgia, unexplained generalised muscle weakness, migratory arthralgia without joint swelling or redness, swollen or painful lymph nodes. The sensitivity at this level was 76.9% whilst specificity was 88.0%.

A two-level case-definition model is therefore proposed - the first to enable the utilisation of a sensitive case definition within a broader definition, and the second to allow a more specific case definition that identifies mainly cases with substantial extent and severity. The findings support the use of the model as a potential tool for public health needs assessment and recommendations are made for the definition to be verified in a large scale study.

From an epidemiological point of view, there is much justification for the use of this approach as it offers a useful alternative to currently existing clinical research definitions of CFS/ME.

Thesis Advisers

Internal: Professor Selena Gray (supervisor), Professor John Duffield and Dr Paul White

External: Dr Derek Pheby (formerly internal), Dr Luis Nacul

Acknowledgements

A lot of people have contributed to this work. I would like to thank my advisors whose tireless efforts in the taking the time to go through drafts, excellent ideas and helpful suggestions have allowed me to bring this process to fruition.

First of all, I thank Professor Selena Gray for her thorough supervision and for consistently encouraging me throughout my doctoral work. She has been a truly wonderful mentor and I am lucky to have worked with her.

I also thank Professor John Duffield my Director of Studies for his kind support and understanding. He played a pivotal role in bringing this project to a successful conclusion and ensured the continuity of the Faculty of Applied Sciences funding for the research without which this project would have never come to be.

In addition, my appreciation should go to Dr Paul White for providing statistical expertise and editing vital aspects of this thesis.

I should not forget to thank Dr. Luis Nacul for enlightening me on aspects of the work.

Extra special thanks go out to Dr. Derek Pheby who initiated the whole project, provided useful information for the understanding of the research, and answered my questions at the start of my work, when I was still ‘new’ in the area of CFS/ME.

I am also grateful to the Faculty of Applied Sciences at the University of the West of England who made available the funding for this work and thus showed incredible support even though CFS/ME is not a specialty area of the Faculty. I should also thank Ms Vicky Elvins for doing everything she could to make my life as a student in the Faculty easier.

My special thanks must go to the members of the expert panel Dr Jeannette Naish, Dr Andrew Wright and Dr Paul Nickson. Without their efforts, this project could not have come to fruition. I also thank the General Practice Research Framework who allowed me easy and timely access to the GP members that played an important role in this study.

I would also like to thank my dear parents, Professor and Mrs JAT Ojo who encouraged me to press on with my education and supported me. My special thanks to my siblings particularly Bunmi and Bola who gave of their time to baby-sit for me during my long trips to Bristol.

Finally, I want to thank my husband and son, Femi and Foluso for their support, understanding and tolerance through out the course of the research. I am eternally grateful to God for granting me the grace and fortitude to complete the course.

Academic presentations

Preliminary results from this study were presented at the 2nd North American Congress of Epidemiology (21 June 2006) and the IEA-EEF (European Epidemiology Federation of the International Epidemiological Association) European Congress of Epidemiology 2006. It will be written up for dissemination in an academic journal.

Table of Contents

List of Tables

List of Figures

Definitions and acronyms

To ensure a clear understanding of some of the terms used throughout the thesis the following acronyms are offered. A list of definitions and descriptions of the CFS/ME criteria used in the study are given in Appendix M.

Acronyms

AfME	Action for ME
CAS	Central Allocation System
CDC	Centers for Disease Control and Prevention
CFS/ME	Chronic Fatigue Syndrome
CF	Chronic Fatigue
CMO	Chief Medical Officer
CRIGS	Centre for Research Innovation and Graduate Studies
DA	Discriminant Analysis
FM	Fibromyalgia
GAD	Generalised Anxiety Disorder
GP	General Practitioner
GPRF	General Practice Research Framework
IOM	Institute of Medicine
MCS	Multiple Chemical Sensitivity
MDA	Multiple Discriminant Analysis
MDD	Major Depressive Disorders
ME	Myalgic Encephalomyelitis
MRC	Medical Research Council
MREC	Multicentre Research Ethics Committee
NMH	Neurally Mediated Hypotension

NPV	Negative Predictive Value
ONS	Office for National Statistics
PCT	Primary Care Trust
PIFS/PVFS	Post Infectious Fatigue Syndrome/Post Viral Fatigue Syndrome
PLR	Positive Likelihood Ratio
PPV	Positive Predictive Value
ROC	Receiver Operator Characteristic
SBV	Sum of Binary Variables
SD	Somatisation Disorder
SRNs	Study Reference Numbers

Chapter 1: Purpose and scope of thesis

1.1. Introduction

Chronic Fatigue Syndrome (CFS) also referred to as Myalgic Encephalomyelitis (ME) is defined by severe fatigue of at least 6 months' duration that interferes substantially with occupational, educational, social, or personal activities, is not alleviated by rest, and cannot be explained by another medical or psychiatric condition (Solomon, Reeves 2004). The commonly reported symptoms of CFS/ME include severe, disabling fatigue, post-exertional malaise, muscle and/or joint pain, sleep disorders, neuro-cognitive dysfunction, autonomic, neuroendocrine and immune manifestations (Department of Human Services, SA. 2004).

CFS/ME affects all age-groups and cuts across socio-economic, racial and ethnic barriers. Although both sexes are affected, there appears to be a higher predisposition amongst females (Jason et al. 1999). Despite intensive studies utilising various clinical and molecular biomedical approaches, no single pathogenic mechanism or general risk factors have been identified; consequently the definitive aetiology of CFS/ME remains unknown.

There is evidence that CFS/ME is heterogeneous in nature (Craig, Kakumanu 2002b) and that it exists simultaneously with other medical conditions (Jason, Taylor & Kennedy 2000). It is not easily distinguished from those conditions which also have chronic fatigue as a major symptom characteristic e.g. depression, Lyme disease, fibromyalgia or cancer (Gaudino, Coyle & Krupp 1997).

Clinical diagnosis of CFS/ME is usually made by exclusion of medical and psychiatric conditions (The Royal Australasian College of Physicians Working Group 2002). The lack of biological markers in differentiating CFS/ME cases from other conditions has led

to the use of clinical criteria or diagnostic case-definitions in CFS/ME research. As a result, much work in this area has been undertaken in producing clinical criteria to help clinicians diagnose CFS/ME. The reduced focus on epidemiological research has meant the use of non-empirically derived case-definition models in CFS/ME epidemiological studies.

The most recent case-definition for CFS/ME is a clinical definition proposed by the Canadian Expert Consensus Panel and published in 2003 (Carruthers et al. 2003).

Although there is no cure for CFS/ME, a number of behavioural and pharmacological approaches are used for the management of the condition (Bagnall et al. 2002). In the UK, work is being undertaken by the National Institute of Health and Clinical Excellence to produce guidelines for clinical diagnosis and management of CFS/ME which are due to be formally released in April 2007.

1.1.1. Why is an epidemiological case-definition for CFS/ME needed?

Public health research in relation to CFS/ME in the past focused mainly on the prevalence and aetiology but nevertheless, lagged behind clinical research.

Measuring the prevalence of CFS/ME is currently a challenge because of the different case-definitions used in epidemiological studies which have produced non-comparable data sets. In addition to the 2003 Canadian case-definition (Carruthers et al. 2003), other popular case-definitions of CFS/ME are the 1988 and 1994 CDC (Holmes et al. 1988, Fukuda et al. 1994) and the Australian and Oxford case-identification criteria. The problems in comparing different public health data sets have been attributed to the inconsistency in the use of these case-definitions, differences in populations surveyed and the research methods employed (Mulrow, Ramirez & Cornell 2001). This has limited efforts to provide adequate health services and effectively target available resources to CFS/ME sufferers with the greatest needs.

The review paper published by the NHS Centre for Reviews and Dissemination, University of York stated that, "current UK estimates of prevalence of CFS/ME range from 0.4% to 2.6%" (Bagnall et al. 2002). However the true extent of CFS/ME in the UK is yet to be formally assessed. The prevalence estimates worldwide vary widely from 0.007% to 2.8% in the general adult population and from 0.006% to 3.0% in primary care or general practice (Afari, Buchwald 2003) indicating that CFS/ME may be a public health burden (Reyes et al. 2003). If prevalence estimates are used from the large numbers of people affected by this condition, the reduced quality of life experienced and increased use of health care services, mean that CFS/ME would be a significant economic burden to society in lost productivity and health care costs (McCrone et al. 2003, Reynolds et al. 2004).

1.2. Policy background

CFS/ME has become known as a politically controversial topic. Up till 2002 there was no national policy or dedicated financial support for CFS/ME research in the UK. Although private efforts and patient groups succeeded in developing local policies to support and fund small-scale research in this field, there was a need to develop and implement a concerted and comprehensive CFS/ME policy agenda. As a result, the Chief Medical Officer (CMO) convened a working party in 1998 to produce guidelines for the diagnosis, treatment and care of CFS/ME patients. In the final report of the working party to the Department of Health, the group highlighted the urgent need for research in the aetiology, epidemiology, natural history spectrum, subgroups and pathogenesis of CFS/ME (CFS/ME Working Group 2002). Subsequently, the Department of Health asked the Medical Research Council (MRC) to develop a broad strategy for advancing biomedical and health services research on CFS/ME.

The MRC's strategy published in 2003 identified the following area as priorities for CFS/ME research: the development of an epidemiological framework for research, co-

morbidity, natural history and outcome of illness (MRC CFS/ME Research Advisory Group 2003).

In another report from the MRC CFS/ME research workshop held on 10 September 2003, it was concluded that:

- 'None of the existing UK epidemiological resources alone were sufficiently large to undertake research on CFS/ME.
- The current prevalence of CFS/ME was too low to allow the use of existing epidemiological UK cohorts. The use of patient record databases such as the General Practice Research Database, and the ONS study Health Survey for England and the Scottish Health Survey in studies would require a broader inclusion criteria e.g. fatigue or sleep disorders to obtain an adequate study sample size.
- There were problems around incompleteness of data and accuracy of existing databases. Changes in the incidence and prevalence of recorded symptoms and diagnoses could be shown to change with time, and consequently historical data would only be informative about diagnostic trends, as opposed to the actual illness (Medical Research Council 2003).

1.3. Aims and objectives of the thesis

The current thesis aims to empirically derive an epidemiological case-definition to identify features which distinguish people with CFS/ME from those without CFS/ME or with other chronic fatigue illnesses.

1.3.1. What are the guiding rules and methodology for developing the epidemiological case-definition for CFS/ME?

Wegman et al (1997) provided a list of criteria for successful case-definitions which are shown below. The case-definition should

(i) 'Establish that the complex of symptoms and other findings are sufficiently different from recognized disease entities i.e. discriminant validity.

(ii) Ensure that the boundaries of the case-definition are not too narrow or too broad to exclude a common aetiology.

(iii) Ensure that the condition can be observed and confirmed by a broad range of specialists in that field.

(iv) Attempt to include considerations of cause and effect, e.g. common exposures, susceptibilities, or demographics

(v) Recognize the social, financial, and political pressures that promote or discourage acceptance of a new category' (Institute of Medicine 2000).

The thesis will take into consideration these guidelines in the methods used to develop the case-definition.

In the methodology for developing the case-definition, current case-definitions for CFS/ME were reviewed and drafted into a checklist. Questionnaires based on this checklist and demographic questions were distributed to General Practitioners (GPs) in the UK for completion. Following return of the forms, an expert reference group was asked to identify cases and non-cases of CFS/ME and statistical analyses undertaken to validate the resulting case-definition.

1.3.2. What are the specific objectives of the thesis?

The main objective of the thesis was to determine those clinical features which assign majority of CFS/ME cases studied to the correct group. These constituted *de facto* the epidemiological case-definition.

Secondary objectives included:

(i) Identifying subgroups on the basis of the clinical manifestations of their illness.

(ii) Assessing the impact of the clinical research definitions on ascertainment and establishing a pragmatic basis for evaluating previous epidemiological work, undertaken using the clinical research definitions.

(iii) Assessing how far GPs' diagnoses are consistent with current definitions and specialist opinion.

(iv) Providing descriptive information on the demographic characteristics of cases.

Limitations to the proposed study

(i) Due to the largely retrospective nature of the study it would not be possible not to assess disease progression or to determine whether psychiatric conditions such anxiety disorder and depression existed before or after the main symptom complex was established. These conditions could have developed as a consequence of CFS/ME.

(ii) The study is largely general practice based and severely ill patients not managed by GPs may be missed. Hence the study conclusions may only be representative of the general practice attendees.

Assumptions include:

(i) GPs records are reasonably complete and the questionnaires were filled in as accurately as possible.

(ii) Other diagnosable and treatable conditions such as hypothyroidism and anaemia occurring in the study population were resolved and thus not responsible for the chronic fatigue illness, in the absence of a diagnosis being made by the GP for cases where such conditions presented.

(iii) A ‘yes’ response on the proformas completed by the GPs implied the definite presence of a clinical sign, symptom or condition whether or not corroborated by laboratory evidence (where required).

(iv) Clinical signs and symptoms were assessed as being either reported or not reported because of the likelihood that information requiring specialised knowledge or detailed assessments of symptom severity and mode of onset would not be available within general practice records for most cases where symptoms were reported.

Subsequent chapters in this thesis will describe in greater detail:

(i) How CFS/ME is defined, diagnosed, and classified and what is known about its aetiology.

(ii) Prevalence studies, the natural history and incidence of CFS/ME.

(iii) The consequences, co-morbidities and relationships (including idiopathic fatigue), and public health burden associated with CFS/ME.

(iv) The general management of CFS/ME patients.

1.3.3. Outline of the thesis

The rest of the thesis is organised as follows:

Chapter two discusses the definitional issues.

Chapter three presents a review of relevant literature.

Chapter four describes the methods employed in the research study.

Chapter five provides the details of the results obtained from the study and analysis of the results.

Chapter six discusses the results.

Chapter seven provides the conclusion and recommendations.

Chapter 2: Definitional issues and the nature of CFS/ME

2.1. Nomenclature and timeline

The term ‘syndrome’ is reserved for a reproducible set or cluster of symptoms, signs, and/or laboratory tests, without known pathology or aetiology (Scadding, 1996). The term ‘Chronic Fatigue Syndrome’ first appeared in March 1988, when the CDC acknowledged a collection of symptoms known as Chronic Fatigue Syndrome, and developed the first widely publicised case-definition.

Prior to this, CFS/ME had been known by a series of names which included neurasthenia, Post Viral Fatigue Syndrome and Icelandic disease. There were differences in opinions as to whether these conditions were the same entity as CFS/ME or closely related variants. Other terms used to describe CFS/ME included chronic fatigue and immune dysfunction syndrome (popular term in the United States) and Icelandic disease. CFS/ME was also thought to bear a resemblance to the nineteenth century descriptions of a condition labelled as neurasthenia (Institute of Medicine 2000).

CFS/ME is a controversial diagnostic entity partly because of the unknown aetiology and pathogenesis. There are different professional views on its name and what does and doesn’t constitute CFS/ME. In addition, the number and type of symptom criteria required to be considered as a case of CFS/ME varies to a large extent. There is also disagreement over expressions used to describe the characteristic symptoms of CFS/ME. Definitional issues are discussed further in chapter 3 of this thesis under case-definitions for CFS/ME.

2.1.1. Developing a classification system

'A case-definition is a set of standard criteria for deciding whether a person has a disease or other health-related condition (U.S. DHHS-CDC 1998). A standard case-definition ensures that every case of the disease is diagnosed in the same way, regardless of when or where it occurred, or who identified it and enables comparability across differed data sets.' A case-definition typically contains a mix of clinical, laboratory, and/or epidemiologic criteria that constitute evidence of illness (U.S. DHHS-CDC 1998).

Public health or epidemiological case-definitions are not usually designed or suitable for making clinical diagnoses and vice-versa. The purpose for classifying the occurrences of a condition may vary. In some cases, case-definitions are generally used to demonstrate that patients are affected by a unique clinical entity that is distinct from all other established clinical diagnoses. They are usually developed primarily to facilitate research and surveillance. They are a starting point for further studies of defined patient populations and understanding of aetiology, risk factors, and natural history of illness which are crucial for public health (Institute of Medicine 2000). Because case-definitions seek to formulate criteria that effectively identify and distinguish a new patient population from patient populations with recognised diagnoses that are often similar, they do not rely on laboratory test results alone, since organisms are sometimes present without causing disease (U.S. DHHS-CDC 1998).' They take into consideration the advice of expert panels weighing the relevant body of research, and may include quantitative techniques' (Ismail et al. 1999).

Evidence from biomedical research combined with social factors, have the potential to influence the recognition, classification, and definition of disease (Rosenberg, Aronowitz & Wessely et al., 2000). This process begins with detection of patients whose symptoms cannot be explained readily by existing diagnoses, hence the widely used term "unexplained" symptoms or illness. Clinicians or epidemiologists then look for patterns or clusters of symptoms that occur together in the same patient and across many patients.

When patterns of symptoms are detected, experts formulate a working “case-definition” that establishes classification criteria for a potentially new syndrome.

2.2. Aetiological basis of CFS/ME

2.2.1. What causes CFS/ME and what are the risk factors for developing it?

The cause(s) of CFS/ME remain unknown. It was once thought that CFS/ME was a type of primary affective and/or somatoform disorder (Jason et al. 1997). This view predicted that any derived sub-groups would differ in terms of severity, but not on other independent illness or laboratory markers.

Another school of thought was that CFS/ME patients contained a subgroup of subjects with `acquired neurasthenia' which could be validated as an independent entity by detecting differences in clinical or laboratory characteristics (Hickie et al. 1995).

To date neither view has been validated using empirical methods. More recently theories of aetiology have been founded on infectious, immunologic, neurologic and psychiatric bases.

2.2.2. Infectious aspects

CFS/ME is also described as a flu-like illness. Post infectious fatigue and chronic immune activation due to acute infection from a non-specific pathogenic agent (most likely a virus) are amongst the theories postulated to explain the cause of CFS/ME (Craig, Kakumanu 2002a).

Linder et al. (2002) used artificial neural networks to classify patients with chronic fatigue (including CFS/ME and idiopathic chronic fatigue), lupus erythematosus, and FM

(Linder et al. 2002). Those chronic fatigue symptoms that had the highest accuracy were “acute onset of symptoms” and “sore throat”, which appears to support the hypothesis of an infectious etiology (Jason et al. 2005). There have been reports of influenza type symptoms and the presence of an infection prior to the onset of clinical symptoms in other studies.

Viruses are the main infective agents ‘proposed alongside transient traumatic conditions, stress and toxins to trigger but not necessarily sustain the development of CFS/ME.’ Infectious mononucleosis was once thought to be linked to the causation of CFS/ME but the theory was discarded after the discovery of elevated Epstein-Barr virus (EBV) titres, (prior infection), in people without CFS/ME (Gold et al. 1990). Viruses linked to CFS/ME include the Coxsackie virus, human herpes virus 6, cytomegalovirus, measles, and the human T-cell lymphotropic virus [HTLV-II]). There is however no evidence to substantiate causation or persistence of these infectious agents in CFS/ME or the view that CFS/ME is a contagious disease.

2.2.3. Immunologic aspects

The link between immunological mechanisms and CFS/ME appears to be validated by recent research. Several immune system patterns observed in CFS/ME patients have been said to be similar to a host response to a virus. In addition, there have been inconsistent reports of allergies and elevated immune complexes (Bates et al. 1995). Studies attempting to identify abnormalities in circulating immune complexes indicate that patients with CFS/ME can show:

i. Different lymphocyte and cytokine profiles and largely inappropriate production of cytokines.

ii. Increased numbers of CD8+ activated “cytotoxic” T cells (Buchwald et al. 1992)

iii. Low natural killer cell function (Klimas et al. 1990).

There is no evidence to suggest however that CFS/ME patients are more susceptible to tissue damage common in autoimmune diseases, opportunistic infections or increased risk of malignancy resulting from a compromised immune system.

There is also a lack of clarity on the role of a low molecular weight protein in an antiviral pathway (the RNase-L pathway). This novel protein was found to occur more frequently in CFS/ME patients than in healthy people, or people with depression or fibromyalgia and on that basis wasproposed as a diagnostic test for CFS/ME (De Meirleir et al. 2000/2). Gow et al. (2001) in contrast found that patients with CFS/ME showed no significant activation of this pathway (Gow et al. 2001).

2.2.4. Neurological and endocrine aspects

The neuroendocrine basis for CFS/ME focuses on the role of the hypothalamic-pituitary-adrenal axis (HPA) (Evengard, Schacterle & Komaroff 1999). According to Komaroff (2000), “the leading model of CFS/ME pathogenesis is rooted in scientifically identified abnormalities in the central nervous system and the immune system, which influence and alter the function of the other in a reciprocal cycle” (Komaroff 2000).

The evidence for the theory was derived from studies reporting lower than normal levels of circulating cortisol in CFS/ME patients in response to physical and emotional stress (Demitrack, Crofford 1998). This coupled with increasing immune activation have been hypothesised as a potential cause of brain dysfunction whereby brain cells and other immune system cells receive messages which could lead to fatigue, cognitive dysfunction, enhanced sense of pain, hormonal dysregulation and other features of CFS/ME (Komaroff 2000). This theory has since been questioned as a result of more recent findings from studies such as undertaken by Inder et al. (2005) which refute the theory of an aetiological role for HPA axis in the symptoms of CFS/ME (Inder, Prickett & Mulder 2005).

The role of the nervous system in CFS/ME has also been reviewed extensively by Freeman et al. (1997) and studied using diagnostic imaging. The results of such studies suggest the presence of neurologic abnormalities in CFS/ME such as alterations in measures of sympathetic and para-sympathetic nervous system (Freeman, Komaroff 1997/4) and function cerebral lesions in white matter, (predominantly in the frontal lobes), impaired regional cerebral blood flow (Craig, Kakumanu 2002a).

Neurally Mediated Hypotension (NMH) is an autonomic manifestation defined as a 30 mmHg drop in systolic (or a 15 mmHg drop in diastolic) blood pressure (attributed to low blood volume or excessive venous pooling in the extremities) in response to an orthostatic challenge such as standing upright (Rowe, Calkins 1998/9/28). There are hypotheses relating to the role of NMH in CFS/ME. These have resulted from investigations such as the observations made of an overlap between CFS/ME and patients with NMH by Bou-Holaigah et al. (1995) who conducted research to determine whether disturbances in the autonomic regulation of blood pressure and pulse (NMH) were common in CFS/ME patients (Bou-Holaigah et al. 1995). Although the association between CFS/ME and NMH has been reported in other studies (De Lorenzo, Hargreaves & Kakkar 1997, Rowe, Calkins 1998/9/28) there is still no evidence to validate NMH as a cause of CFS/ME.

2.2.5. Other theories

There are no validated or proven specific diagnostic tests for CFS/ME. The inability to identify specific causation agents and suitable diagnostic tests has been attributed to the multi-symptom and multi-system nature of CFS/ME. In addition, there are many illnesses that manifest chronic fatigue as a symptom and this has led to the need for exclusion of such conditions before a diagnosis of CFS/ME can be made. Findings of some CFS/ME studies involving twins suggest that genetic factors may play a role in the development of CFS/ME (Torpy et al. 2004, Walsh et al. 2001).

2.3. Epidemiological Assessment of CFS/ME

2.3.1. Prevalence studies

'Prevalence' is the main epidemiological measure used to describe how commonly a disease occurs in a population. It is a percentage in a population of individuals having a condition, which satisfies a specific case-definition of the condition.

There are inconsistencies in the prevalence rates for CFS/ME because like any other disease or condition, the prevalence score is totally dependent on the case-definition employed in a particular situation.

It has been shown that the use of different criteria in CFS/ME epidemiological research is responsible for the underreporting of cases and underestimation of the prevalence of the condition in some areas (Pheby 2000). Prevalence for CFS/ME rates vary widely from 0.007% to 2.8% in the general adult population and from 0.006% to 3.0% in primary care or general practice (Afari, Buchwald 2003).

Between 1989 and 1993, the Centers for Disease Control (CDC) estimated that between 4.0-8.7/100,000 persons 18 years of age or older had CFS/ME and were under medical care in the United States (Afari, Buchwald 2003). This study had limitations arising from the lack of selective randomisation of sites; hence the figures were underestimates of projections which were not generalisable. Findings from surveys that have involved at least 100 adult participants suggest the prevalence of CFS/ME in community populations is less than 1 percent (Mulrow, Ramirez & Cornell 2001).

In addition to the use of non-standardised clinical/diagnostic criteria, factors contributing to the wide ranging prevalence estimates include differences in the population surveyed, the research methodology employed and poor response rates in some studies.

Since very few UK studies focus on the epidemiology of CFS/ME, uniform case identification criteria are needed to enable better understanding of CFS/ME and increase the comparability of different data sets.

Table 1 presents prevalence estimates from different data sources, methods and case-definitions, which are discussed in the literature review section (chapter three) of this thesis.

Table 1 Prevalence estimates of CFS/ME

Author (year of publication)	**Country (region or worldwide)**	**Population studied**	**Study size**	**Age**	**Prevalence (per 10^5)**	**Case identification criteria**
Lloyd et al (1990)	Australia	Primary care	114000	Not specified	39.6	Chronic fatigue of at least 6 months, significant disability in usual daily activities
Buchwald et al. (1995)	USA	Primary care	3066	> 18 years	75-267	The 1988 CDC case-definition for CFS/ME
Lawrie et al (1995)	UK	Primary care	1000	> 18 years	560	Oxford criteria
Reyes et al. (1997)	USA	Community based and tertiary care	565	> 18 years	4.0-8.7	The 1988 CDC case-definition
Wessley et al. (1997)	England	Primary care	2376	> 18 years	2600	The 1994 CDC case-definition
Jason et al (1999)	USA	Community based	28673	> 18 years	420	The 1994 CDC case-definition
Reyes et al (2003)	USA	Community based	90316	> 18 years	235	The 1994 CDC case-definition for CFS/ME
Bierl et al (2004)	USA	Community based	884	> 18 years	1197	The 1994 CDC case-definition

2.3.2. Incidence

Very few studies exist on the incidence of CFS/ME in the general population. Reyes et al. (2003) reported a one year incidence of CFS/ME of 180 per 100 000 people (Reyes et al. 2003).

2.3.3. Public health burden

CFS/ME affects all age-groups and cuts across socio-economic, racial and ethnic barriers impacting considerably on social, economic, educational, and health care delivery systems. Although both sexes are affected by the condition, there is a higher predisposition amongst females (Reyes et al. 2003). CFS/ME has been associated with a reduction in the quality of life and with high utilisation of health care services. The debilitating nature of the illness manifests as personal and occupational disability. Health care workers are the most commonly affected occupational group (Bagnall et al. 2002).

The magnitude of the economic impact of the condition documented in past research studies indicate that the occupational or employment status of an individual affected by CFS/ME alters significantly after the onset of illness. In addition, unemployment rates for CFS/ME patients have been found to be higher when compared with overall unemployment rates in the population.

2.4. Clinical Management

2.4.1. What are the effective therapies for CFS/ME?

The most common means of evaluating CFS/ME includes a comprehensive history of the patient's condition, physical examination and mental state assessment.
A diagnosis of CFS/ME is usually made only after alternative medical and psychiatric causes of fatiguing illness have been excluded (Institute of Medicine 2000).

There is no laboratory test that can validate a diagnosis of CFS/ME, as no pathognomonic medical characteristic exists which is common amongst patients. Laboratory investigations are mainly useful in excluding other causes of fatigue. The basic screening tests include Complete Blood Picture (CBP); Erythrocyte Sedimentation Rate (ESR); fasting Blood Sugar Level (BSL); alanine aminotransferase (ALT), albumin, alkaline phosphatase (ALP), blood urea nitrogen (BUN), calcium, creatinine, electrolytes, globulin, glucose, phosphorus, thyroid stimulating hormone (TSH), total protein, transferrin saturation, and urinalysis (The Royal Australasian College of Physicians Working Group 2002).

CFS/ME has no known cause or cure. Management of CFS/ME patients is symptom-based and includes pharmacotherapy and non-pharmacological therapy sometimes borrowed from related fields (e.g., sleep medicine, autonomic nervous system abnormalities, endocrinology, gastrointestinal illness, neurocognitive therapy) (The Royal Australasian College of Physicians Working Group 2002). This is because there is no specific treatment for CFS/ME. The objectives of therapy are usually to help the patient develop realistic goals and expectations through education, to provide symptomatic relief, and to preserve and improve the patient's ability to function.

Examples of pharmacological therapies in the management of CFS/ME are medications to improve sleep or relieve pain, use of dietary supplements, antidepressants, corticosteroids, immunotherapy. Examples of non-pharmacological therapies in the

management of CFS/ME acupuncture, cognitive behavioural therapy and moderately controlled exercise. Cognitive Behavioral Therapy (CBT) and Graded Exercise Therapy (GET) have been identified as potentially effective therapeutic methods (Bagnall et al. 2002). Other therapies reported in the literature include antiviral, complementary and a combination of treatments. There is increasing evidence to show that response to treatment varies by the severity and duration of illness.

While this chapter has aimed to describe the purpose and background to the research, the next chapter will review the case-definitions and describe in greater detail, the heterogeneity of CFS/ME and symptom criteria associated with the case-definitions.

3. Review of the related literature on CFS/ME case-definitions

3.1. Introduction

This chapter presents a review of the background literature on research and clinical case-definitions for CFS/ME. It describes in brief the individual symptoms reported in the definitions. Debilitating post-exertional fatigue is a key feature of CFS/ME. Fatigue itself has been defined as ‘a state of increased discomfort and decreased efficiency resulting from prolonged or excessive exertion.’ As a symptom, fatigue has a complex phenomenology, relates to numerous potential aetiologies, and accompanies a broad array of physical and psychological comorbidities (Portenoy 2003). Other symptoms reported in CFS/ME case-definitions are listed and defined in Appendix M.

3.2. Case-definitions for CFS/ME

There are several case-definitions for CFS/ME. The most commonly referenced CFS/ME criteria include the 1994 US Centers for Disease Control (CDC), Oxford, Australian and the most recent Canadian case-definitions (Appendix F).

The earliest documented account of CFS/ME case-identification criteria was back in 1955 when an outbreak of a mysterious illness at the Royal Free Hospital, London prompted Ramsay (1981 and 1988) to publish criteria describing a CFS-like illness using the term Myalgic Encephalomyelitis (Hyde, Goldstein & and Levine 1992, Ramsay 1981, Ramsay 1988).

Other case identification criteria specific to ME have been proposed by Dowsett (Dowsett 1992, Dowsett et al. 1990)'. Jason et al (2003) compared the 1994 CDC criteria and the Dowsett criteria and found that those meeting the latter criteria, in contrast to those meeting the 1994 CDC case identification criteria, had significantly poorer neurological, neuropsychiatric, fatigue/weakness, and rheumatologic symptoms than those with chronic fatigue explained by psychiatric conditions (Jason et al. 2003). Thus amongst some researchers it is thought the ME is a more severe form of CFS or a clinically distinct and separate entity.

Although the 1994 CDC case-definition is the most widely used, to date none of the case-definitions has been proven to have pre-eminence over another in epidemiological studies. Details of each of the key case-definitions are given below.

3.2.1. The Canadian consensus definition

The Canadian case-definition comprises broad criteria developed primarily for clinical use (Carruthers et al. 2003). It employed an evidence based approach to its development and was published in 2003. Under this definition for CFS/ME, a case was required to have an illness that persisted for at least 6 months. In addition, there should be a marked degree of new onset of unexplained, persistent, or recurrent physical or mental fatigue that substantially reduces activity level. Post-exertional malaise must occur with loss of physical or mental stamina, rapid muscle or cognitive fatigability, usually with 24 hr or longer to recover.

Other requirements included unrefreshing sleep or sleep quantity or rhythm disturbance, and a significant degree of arthralgia and/or myalgia (in a small number of patients with no pain or sleep dysfunction and a diagnosis should only be given when these individuals have a classical case with an infectious illness onset) or more neurocognitive manifestations (e.g., confusion, impairment of concentration, and short-term memory).

Further, at least one symptom from two of the following categories was required: autonomic manifestations (neurally mediated hypotension, light headedness), neuroendocrine manifestations (e.g., recurrent feelings of feverishness and cold extremities), and immune manifestations (e.g., recurrent sore throats) (Jason et al. 2004).

When compared with the 1994 CDC case-definition in a subset of individuals experiencing chronic fatigue explained by psychiatric reasons, the Canadian case-definition criteria selected cases with less psychiatric co-morbidity, more physical functional impairment and more fatigue/weakness, neuropsychiatric and neurologic symptoms (Jason et al. 2005).

Limitation(s) of the Canadian case-definition

Prior to the Canadian clinical case-definition, no other CFS/ME case-definitions had incorporated empirical methods during development. A limitation of the Canadian case-definition was that it did not define the conditions that could result in fatigue. The extent to which it discriminates between CFS/ME patients and those with other fatiguing illnesses is not known.

3.2.2. The 1988 CDC case-definitions

The first CFS/ME case-definition in the US was developed through a CDC consensus panel in 1988 and intended to be a guide in evaluating patients with chronic fatigue of unknown cause (Holmes et al. 1988). Under this definition, a case was determined by the presence of 2 major and at least 8 of 11 minor symptom criteria or at least 6 of 11 minor symptom criteria and 2 of 3 physical criteria (see Appendix F). De Becker et al. (2001) found that the CFS/ME patients fulfilling the Holmes criteria have an increased symptom

prevalence and severity of many symptoms in comparison to the Fukuda criteria (De Becker et al. 2001).

Major symptom criteria

The 2 major criteria comprising this case-definition included:

(i) A new onset to persistent, relapsing, debilitating fatigue or easy fatigability in a person with no previous history of similar symptoms that is unresolved by bed rest and severe enough to reduce or impair the patient's average daily activity below 50 percent of the premorbid activity level for a period of at least 6 months.

(ii) The absence of clinical conditions capable of causing similar symptoms upon investigation through history, physical examination and laboratory tests. Exclusionary medical conditions included malignancy, infection, drug use (prescription and illicit), toxic agents, chronic inflammatory, neuromuscular, autoimmune, psychiatric, endocrine conditions and disorders of the lung, heart, gastrointestinal system, liver, kidney and blood.

Minor symptom criteria

The minor symptom-related criteria were required to persist or recur over at least 6 months and included:

(i) Mild fever (oral temperature of 37.5-38.6^{0}C if measured by the patient, or chills), sore throat, painful lymph nodes (anterior or posterior cervical and axillary lymph nodes), unexplained muscle weakness, prolonged (24 hours or greater) generalised fatigue after levels of exercise that would have been easily tolerated in the patient's' premorbid state.

(ii) Muscle discomfort or myalgia, new or different generalised headaches, migratory arthralgia without joint swelling or redness, neuropsychiatric complaints (one or more of the following: photophobia, transient visual scotomata, forgetfulness, excessive irritability, confusion, difficulty with thinking, depression and inability to concentrate), sleep disturbance (hypersomnia or insomnia), development of the symptom complex over a few hours to a few days.

Minor physical criteria

(i) These included lymphadenopathy, non-exudative pharyngitis (sore throat), low grade fever- oral temperature between 37.6^{0}C and 38.6^{0}C or rectal temperature between 37.8^{0}C and 38.8^{0}C[17].

Limitations of the 1988 CDC definition

The limitations of this definition are presented as follows:

(i) The primary characteristic of this CFS/ME case-definition ‘fatigue’ is of an abstract nature and doesn’t distinguish CFS/ME from other types of unexplained fatigue or define a distinct group of cases. As stated by Hyde (1992), “fatigue is a normal and pathological feature of everyday life and a common feature of major medical and psychiatric disease”.

(ii) As studies have demonstrated that some of the exclusionary clinical conditions are closely linked to the outcomes of CFS/ME, cases could be misrepresented or underreported in prevalence studies.

(iii) Some studies have reported a high prevalence of neuropsychiatric disorders in CFS/ME patients. The inclusion of neuropsychiatric dysfunction as a minor symptom criterion amongst eleven criteria of which eight is required for the case-definitions suggests the possibility of excluding large number of CFS/ME patients who have neuropsychiatric dysfunction with some other symptoms of chronic fatigue.

(iv) Although there have been reports of clusters of CFS/ME-like illness in the US, there is no evidence to indicate that CFS/ME is a contagious condition. Symptom criteria such as lymphadenopathy, non-exudative pharyngitis which are common manifestations of infectious diseases may not be important discriminating factors.

3.2.3. The 1994 CDC case-definition

Due to the limitations outlined above, another CDC consensus panel (Fukuda et al.) was set up to revise the 1988 CFS/ME case-definition. The second CDC CFS/ME definition was developed primarily for research rather than diagnostic purposes and published in 1994. It incorporated major elements of the 1988 definition. Under the new definition a case was required to fulfil the following criteria:

(i) Severe chronic fatigue of at least 6 months or longer with other known medical conditions excluded by clinical diagnosis.

(ii) Four (4) or more of the following symptoms concurrently: substantial impairment in short term memory or concentration, sore throat, tender lymph nodes, muscle pain, pain in multiple joints without swelling or redness, headaches of a new type,

pattern or severity, unrefreshing sleep; and post exertional malaise lasting more than 24 hours.

The symptoms must have persisted or recurred during six (6) or more consecutive months of illness and must not have predated the fatigue (Fukuda et al. 1994).

The new case-definition thus differed mainly in respect to:

(i) Absence of the major, minor and physical symptom criteria groupings.

(ii) Decrease in the minimum symptoms required from 8 to 4 and the overall list of symptoms from 11 to 8. This was due to agreement amongst the panel members that multiple symptom criteria "increased the restrictiveness of the Holmes definition without increasing the homogeneity of cases."

(iii) Integration of criteria for non-psychotic disorders.

(iv) Its attempt to distinguish between prolonged fatigue and chronic fatigue. Prolonged fatigue was defined as "self-reported, persistent fatigue lasting one month or longer", and chronic fatigue was defined as "self-reported persistent or relapsing fatigue lasting 6 or more consecutive months" (Fukuda et al. 1994).

Limitations of the 1994 CDC case-definition

The 1994 CDC case-definition has been widely accepted though criticised for lacking specificity in some cases (Jason et al 2001). Although the symptom criteria were found to be relevant in the diagnosis of CFS/ME, the occurrence of post-exertional malaise, cognitive and memory difficulties and unrefreshing sleep did not uniquely discriminate between the CFS/ME and control groups, as individuals in the melancholic depression group also experienced these symptoms with significantly greater frequency than controls (Jason et al. 2001).

Other criticisms include:

(i) The subjectivity of the terms used for criteria in the case-definition. Ambiguity is found in the definition of chronic fatigue (persistent or relapsing, new or definite onset), in the description of the severity of symptoms as ‘present’ or ‘absent’, the meaning of ‘substantial limitation of activity’ (caused by fatigue) and the definition of post exertional malaise lasting more than 24 hours (Jason et al. 1999).

(ii) There was a lack of distinction between CFS/ME and other conditions such as major depressive disorders (MDD), generalised anxiety disorder (GAD) and somatisation disorder (SD). Thus there was a potential for misdiagnosis of CFS/ME for persons with chronic fatigue relating to MDD or GAD or SD because of the overlap of some symptoms (Komaroff et al. 1996).

Both 1988 and 1994 CDC case-definitions lacked an empirical base and relied solely on consensus. In 2003, the CDC published guidelines to clarify ambiguities and to provide recommendations for the use of the 1994 case-definition. The guidelines also lacked an empirical basis and proved complex to apply to basic epidemiological studies. In the guidelines, medical and psychiatric exclusions were classified as permanent or temporary. A non-exhaustive list of permanent medical exclusions was provided which included:

a Organ failure (e.g. emphysema, cirrhosis, cardiac failure, chronic renal failure);

b Chronic infections (e.g. AIDS, hepatitis B or C);

c Rheumatic and chronic inflammatory diseases (e.g. systemic lupus erythematosis, Sjogren's syndrome, rheumatoid arthritis, inflammatory bowel disease, chronic pancreatitis);

d Major neurologic diseases (e.g. multiple sclerosis, neuromuscular diseases, epilepsy or other diseases requiring ongoing medication that could cause fatigue, stroke, head injury with residual neurologic deficits);

e Diseases requiring systemic treatment (e.g. organ or bone marrow transplantation, systemic chemotherapy, radiation of brain, thorax, abdomen, or pelvis);

f Major endocrine diseases (e.g. hypopituitarism, adrenal insufficiency);

g Primary sleep disorders (e.g. sleep apnea, narcolepsy) (Reeves et al. 2003).

Temporary medical exclusions included:

a Effects of medications, sleep deprivation, untreated hypothyroidism, untreated or unstable diabetes mellitus, active infection;

b Pregnancy until 3 months post-partum, breast feeding, major surgeries until 6 months post-operation, minor surgery until 3 months post-operation, and major infections such as sepsis or pneumonia until 3 months post-resolution; sleep disorders which are severe, but not insufficient to explain the severity of the fatigue e.g. restless leg syndrome and periodic limb movement;

c Myocardial infarction, heart failure;

d Morbid obesity.

Permanent psychiatric exclusions included:

a Lifetime diagnoses of bipolar affective disorders, schizophrenia of any subtype, delusional disorders of any subtype, dementias of any subtype, organic brain disorders, and alcohol or substance abuse within 2 years before onset of the fatiguing illness.

b Major depressive disorder with psychotic or melancholic features, anorexia nervosa, or bulimia which have been resolved for more than 5 years before the onset of the current chronically fatiguing illness.

3.2.4. The Oxford case-definition

The Oxford case-definition was developed in 1991. This definition required mainly the presence of chronic fatigue and cognitive impairment in order to make a diagnosis of CFS/ME (see Appendix F). It also referred to CFS/ME as being associated with a current infection or following an infection. As a result case-identification criteria for a sub-group of CFS/ME known as Post Infectious Fatigue Syndrome or Post Viral Fatigue Syndrome (PIFS/PVFS) were proposed.

The Oxford definition differed from the other case-definitions in that it was the only case-definition which required a definite onset of illness for a clinical diagnosis of CFS/ME.

Limitations

(i) This definition did not recognise any clinical sign or symptom as characteristic of CFS/ME.

(ii) By including all categories of fatigue and excluding core symptoms cited in other definitions such as neurological symptoms there was a potential for overestimation in prevalence studies.

(iii) It cited fatigue as the principal symptom of CFS/ME for which the Holmes definition was criticised.

(iv) It defined CFS/ME as a syndrome which is not lifelong thus failing to recognise the evidence of lifelong CNS dysfunction in some cases of CFS/ME (Manu, Matthews & Lane 1988).

3.2.5. The Australian case-definition

The Australian case-definition published by Lloyd et al. in 1990, bore some similarity to the 1994 CDC in its main requirement of the presence of chronic fatigue and immune dysfunction for a clinical diagnosis of CFS/ME (Lloyd et al. 1990b). It also required post-exertional malaise, neuropsychiatric symptoms including difficulty with memory and concentration to determine a case of CFS/ME (see Appendix F). However differences exist between the Australian criteria and CDC criteria.

Limitations

It is thought that the Australian case-definition presents a very loose set of criteria for defining a case. The inclusion of neuropsychiatric dysfunction symptoms as mandatory criteria and requirement of the presence of multiple minor symptoms and signs rendered it less restrictive than the 1994 CDC case-definition. In contrast, neuropsychiatric symptoms and post-exertional malaise in the 1994 CDC criteria were optional as they represented symptoms among a group of eight, of which four should be present for a clinical diagnosis of CFS/ME.

3.3. CFS/ME case-definition issues

These clinical case-definitions highlight the heterogeneous nature of CFS/ME particularly clinical heterogeneity. There are some similarities and differences between the case-definitions. Their major similarity lies in the requirement of the presence of fatigue of at least six months. The CFS/ME case-definitions have been developed primarily using consensus methods, and have evolved over time. To date, the validity of these definitions

has been difficult to establish because of the apparent lack of biologic markers for CFS/ME (Mulrow, Ramirez & Cornell 2001). Further the symptom-sharing nature of CFS/ME with other conditions particularly psychiatric disorders complicates the development of an acceptable case-definition for CFS/ME. As highlighted in previous chapters, this is largely due to the difficulty in diagnosing the condition because of the lack of specific pathognomonic signs and the complexity in the measurement of CFS/ME definitional symptoms (Myalgic Encephalomyelitis Research Group for Education and Support 2003).

The commonality amongst findings from research studies evaluating the case-definitions is 'the concept of a condition, characterized by prolonged fatigue and impaired ability to function' (Mulrow, Ramirez & Cornell 2001). With the exception of the Canadian case-definition which presents CFS/ME as a separate diagnostic entity, none of the case-definitions demonstrate pre-eminence over another.

The main differences between the definitions include:

(i) Only the Oxford criteria required a definite onset of illness

(ii) Only the Australian criteria required multiple minor symptoms and signs

(iii) The Canadian criteria selected cases with less psychiatric co-morbidity, more physical functional impairment and more fatigue/weakness, neuropsychiatric and neurologic symptoms when compared with the 1994 CDC criteria thus implying that the CDC 1994 definition, preferentially included patients with psychiatric disorders.

The case-definitions are set out in a table in Appendix F of this thesis.

3.3.1. The World Health Organisation (WHO) International Classification of Diseases (ICD-10)

The World Health Organization ICD-10 is an international standard diagnostic classification for all general epidemiological and many health management purposes. It includes an analysis of the general health situation of population groups, the monitoring of the incidence and prevalence of diseases and other health problems in relation to other variables such as the characteristics and circumstances of the individuals affected. It is primarily used to classify diseases and to enable the storage and retrieval of diagnostic information for clinical and epidemiological purposes (World Health Organisation 2003).

The WHO ICD-10 classification criteria for CFS/ME are varied and not robust enough to distinguish between cases and non-cases of CFS/ME for epidemiological research purposes. The generic term ‘Chronic Fatigue Syndrome’ is not used in its classification, rather it uses related terms- Post-viral fatigue syndrome (PVFS) and neurasthenia. The ICD-10 aims to maintain mutually exclusive individual categories and subcategories thus avoiding the classification of the same condition to more than one rubric.

PVFS is classified as a disease of the nervous system (G93.3) and also referred to as ‘benign myalgic encephalomyelitis’. In contrast, “neurasthenia” is classified under mental and behavioural disorders/neurotic stress related and somatoform disorders as F48.0. The F48.0 code includes a fatigue syndrome which is not PVFS.

The ICD-10 recognised mental fatigue and post exertional fatigue as the two forms of presentation of F48.0 with considerable overlap. F48 also composed of a subset ‘fatigue syndrome’. Accompanying symptoms of F48.0 included dizziness, tension headaches, and feelings of general instability, worry about decreasing mental and bodily well-being, irritability, anhedonia, and varying minor degrees of both depression and anxiety and sleep disorders.

In addition, the ICD-10 criteria lacks precision e.g. F48.0 does not specify the duration of fatigue and is comprised mainly of neuropsychiatric symptoms and thereby portrayed as a primary mental disorder which CFS/ME is not. Further there are no studies which validate these criteria.

3.4. CFS/ME: dimensions and symptoms

At this stage of the review, it is important to highlight that unless otherwise stated the majority of the studies reviewed in the following subsections have used the 1994 CDC case-definition in selecting cases for the studies. Further, most of the studies are neither comparable nor generalisable due to criterion variance, differences in inclusion and exclusion criteria and sample sizes.

Attempts made by to validate CFS/ME case-definition criteria have all yielded different results as shown in the table below.

Table 2 Studies validating the multidimensional nature of CFS/ME

Researchers	Case-definition and Method	Key dimensions identified as part of CFS/ME	Conclusions
Hickie, I et al (1995)	*1994 CDC case-definition* principal components and latent class analyses	(i) Somatoform-type symptoms (ii) Combination of fatigue, neuropsychological symptoms and moderate disability	The separation of CFS/ME patients beyond the two subgroups was unlikely on basis of symptom reports (Hickie et al. 1995).
Nisenbaum et al. (1998)	*1994 CDC case-definition* Factor analysis	(i) Fatigue-mood-cognition symptoms (ii) Flu-like symptoms (iii) Visual impairment	3 factors (symptom dimensions) explained correlations for unexplained fatigue of at least 6 months and 14 interrelated symptoms (Nisenbaum et al. 1998).
Friedberg et al. (2000)	*1994 CDC case-definition* Principal components analysis	(i) Cognitive symptoms (ii) Flu-like symptoms (iii) Neurologic Symptoms	3 symptom dimensions were identified. Cognitive symptoms varied in severity according to the duration of illness (Friedberg et al. 2000).
Jason et al. (2002)	*1994 CDC case-definition* Cluster analysis	All 3 clusters had CFS/ME characterised by: (i) relatively low post-exertional fatigue or (ii) severe post-exertional fatigue and improvement in fatigue following rest (iii) high post-exertional fatigue and fatigue not alleviated by rest.	Three clusters were identified. Cluster 3 contained the highest proportion of individuals with CFS/ME (Jason, and Taylor 2002).
Nisenbaum et al. (2004)	*1994 CDC case-definition* Factor analysis	(i) Musculoskeletal symptoms (muscle pain, joint pain, unusual fatigue after exertion) (ii) Infection symptoms (sore throat, tender lymph nodes) (iii) Cognitive symptoms (difficulty thinking and forgetfulness) mood disorder (iv) sleep disorder	None of the individual symptoms assessed explained CFS/ME as a single entity. All the case-defining symptoms, except severe headaches, constituted the subgroups (Nisenbaum et al. 2003).

In spite of the many criticisms levied against the 1994 CDC case-definition, the studies in Table 2 provide evidence that the case-definition supports the concept of CFS/ME as a multidimensional entity. For each study, there were marked differences in the subgroups identified and the stratification criteria such as illness duration, recovery, severity of psychological morbidity, health service use and CD8 T cell subset counts (Hickie et al. 1995). This suggests that CFS/ME is a condition of multifactorial aetiology possibly overlapping with the symptoms of other unexplained chronic illnesses. In addition, recent trends in analytical studies appear to indicate that post exertional fatigue and cognitive problems should form part of the major criteria for a CFS/ME case-definition (Jason et al. 2000). The following subsections therefore discuss the evidence for specific symptoms and subgroups in the CFS/ME case-definition. Individual symptoms are presented a part of a group of related diseases for clarity where applicable.

3.4.1. Fatigue/muscle weakness

Symptoms of fatigue and weakness in case-definitions include general muscle weakness (or weakness in any muscle of the body) and post-exertional malaise/fatigue.
CFS/ME patients tend to experience more occurrences of generalized muscle weakness than healthy individuals (Jason et al. 2002). Post exertional fatigue in particular has been highlighted as a potential diagnostic marker and a major criterion for CFS/ME (Jason et al. 2000). This supports the initial postulate of case-definitions such as the Australian case-definition (Lloyd et al. 1990a), the Canadian case-definition (Carruthers et al. 2003) and the ME criteria (Dowsett et al. 1990, Dowsett et al. 1994, Ramsay 1981). However, there is no evidence to indicate it can discriminate between CFS/ME and other fatiguing illnesses.

3.4.2. Infection at onset or presentation corroborated by laboratory evidence

Symptoms of infection at onset or presentation include sore throat, swollen and painful lymph nodes, fever or chills. A higher occurrence of infectious symptoms has been reported to occur in CFS/ME patients when compared to healthy individuals (Jason et al. 2002/2).

3.4.3. Impaired cognitive function/ symptoms

Cognitive problems reported to occur in CFS/ME patients include difficulties with short term memory, concentration and information processing. CFS/ME patients are more likely to experience problems with short-term memory, concentration and thinking than healthy individuals. Although past studies demonstrate links between cognitive functioning and CFS/ME (Busichio et al. 2004) they are not really suitable for comparison because these have used small sample sizes and different methodologies. None of these studies provide substantial evidence to support an association between cognitive impairment, depression, anxiety and fatigue in CFS/ME patients (Marcel et al. 1996, Marshall et al. 1997, Michiels and Cluydts 2001).

3.4.4. Neuropsychiatric symptoms

Neuropsychiatric symptoms reported in CFS/ME patients include headaches, depression, excessive irritability and visual disturbances (photophobia, transient visual scotomata). Research studies show that there is a high prevalence of neuropsychiatric

symptoms in individuals with cognitive impairment who may or may not have CFS/ME (Lyketsos et al. 2002). CFS/ME patients presenting with neuropsychiatric symptoms however differ significantly from depressed patients in terms of their cognitive styles and immunologic profiles (Natelson and Lange 2002).

3.4.5. Rheumatological symptoms

Rheumatological symptoms which include muscle pain (myalgia), joint pain (arthralgia), have been reported to occur in CFS/ME patients with significantly greater frequency than healthy individuals (Jason et al. 2002).

3.4.6. Sleep disturbance (hypersomnia, insomnia or unrefreshing sleep)

Sleep disturbance includes all symptoms of unrefreshing sleep, insomnia and hypersomnia. CFS/ME patients have also been reported as having a greater tendency to experience sleep disorders more than healthy individuals (Jason et al. 2002).

3.4.7. Neurological symptoms

Commonly occurring neurological symptoms in CFS/ME patients include orthostatic intolerance/ Neurally Mediated Hypotension (NMH) or other autonomic manifestation with symptoms such as light-headedness, dizziness during and after standing, nausea, fatigue, tremors, breathing or swallowing difficulties, headaches, visual

disturbances, and pallor. The frequency of NMH in CFS/ME patients has not been consistently reported across studies.

3.5. Heterogeneity of CFS/ME and subgroups

This section presents a review of the basis for sub grouping in CFS/ME. CFS/ME shares many similarities with somatoform disorders and neuropsychiatric syndromes. Disorders such as anxiety depression, major depression have been diagnosed in higher proportions of CFS/ME patients than in the general population (Manu, Lane & Matthews 1993). It is thus necessary to clarify these relationships and distinguish CFS/ME from co-morbid conditions because they are potential confounders in CFS/ME research.

As a result of the use of clinical research definitions which have tended to classify CFS/ME in homogenous groups, past studies have portrayed it as a homogenous condition. This has been in spite of the multi-symptom nature of CFS/ME. Research participants have thus been classified accordingly thereby leading to difficulties in identifying commonalities in CFS/ME patients and inconsistent medical findings (DeLuca et al. 1997).

In a study comparing patients meeting the major criteria of 1988 CDC case-definition with healthy controls and groups with multiple sclerosis and depression, it was concluded that adding anorexia and nausea to the case identification criteria and eliminating muscle weakness, arthralgias, and sleep disturbances from the criteria would strengthen the case-definition (Komaroff et al, 1996). This was in contrast to the results of a study based on the CDC 1994 criteria that was undertaken by Jason et al. (2002). The researchers found that the muscle weakness and arthralgias reported in more than half of participants with CFS/ME differentiated them from control groups. Jason et al also found that there was low frequency of occurrence of sleep disturbance, anorexia and nausea and that these did not discriminate between CFS/ME and control groups (Jason et al. 2002).

More evidence is emerging which confirms the heterogeneity of CFS/ME and the existence of possible subgroups on the basis of varying and distinct patterns of symptom severity. Symptom severity is important in epidemiological case-definitions as thorough health needs assessments rely entirely on valid measures of severity of true cases (Williams, Wright 1998). Jason et al. (2000) found that examining symptoms utilising severity criteria was useful in uniquely differentiating CFS/ME from fatigue explained by a psychiatric disorder (Jason et al. 2000).

Although the 1994 CDC case-definition in particular suggested the sub grouping of CFS/ME patients it did not exclude possible subgroups with psychiatric co-morbidity thus reducing its specificity. Kennedy et al (2004) observed clear differences in clinical measures in similar groups of patients, who met the 1994 CDC criteria for CFS/ME and concluded that the sensitivity of the definition could be improved by specifying precipitating factors and/or developing a scoring system for onset factors to improve diagnostic reliability.

Subgroups of CFS/ME have also been identified in a study to define a ‘typology of Chronic Fatigue Syndrome in a medically-evaluated, random community sample’; post exertional fatigue of high severity was the key defining symptom. The two main subgroups emerging from the study were thus classified by firstly severe post-exertional fatigue and fatigue relieved by rest; and secondly severe by CFS/ME symptoms, severe post exertional fatigue and fatigue that is not alleviated by rest (Jason et al. 2000).

Other suggestions for observing sub groups within CFS/ME include:

(i) Clear delineating of precise criteria for diagnosing pure CFS/ME and CFS/ME that is co morbid with psychiatric disorders.

(ii) Differentiation of CFS/ME from other disorders which share some CFS/ME symptoms but are not true CFS/ME cases (Jason et al. 1997).

(iii) Sub grouping patients on the basis of objective clinical signs (Acheson 1959, Hyde, Goldstein & and Levine 1992).

(iv) Assessing symptom severity on a validated scale in a standardized manner, valuable to preserve clinical information (Kennedy et al. 2004/2).

Researchers have advocated sub typing CFS/ME patients during studies to reflect differing socio demographic characteristics, the case-definition utilised, psychiatric co-morbidity, method of case ascertainment, functional disability, and viral, immunologic, neuroendocrine, neurology, autonomic and genetic biomarkers (Jason et al. 2005).'
Recent research however indicates that three main clinical subtypes of CFS/ME may exist, which are based on minor diagnostic criteria. These three subtypes are related to musculoskeletal, infectious and neurological factors (Janal et al. 2006).

3.5.1. Overlapping and comorbid conditions

The symptom-sharing nature of CFS/ME with other conditions, particularly psychiatric disorders, has complicated the development of an acceptable case-definition for CFS/ME. This is largely due to the difficulty in diagnosis arising from the lack of specific pathognomonic signs and the complexity in the measurement of CFS/ME definitional symptoms, as highlighted in previous sections of the thesis.

Studies show that there is marked overlap between symptoms of CFS/ME and fibromyalgia (FM) (Aaron, Buchwald 2001). Other CFS/ME-like illnesses or overlapping conditions reported in patients include: Myofascial Pain Syndrome (MPS), Temporomandibular Joint Syndrome (TMJS), chronic or sub-acute bacterial disease, Irritable Bladder Syndrome (IBS), Irritable Bowel Syndrome, Raynaud's phenomenon, migraine, Sicca syndrome, premenstrual syndrome, Multiple Chemical Sensitivity (MCS), depression and headaches.

Fibromyalgia (FM) and Multiple Chemical Sensitivity (MCS) are the two most common “medically unexplained illnesses”, with symptom profiles similar to CFS/ME (Sullivan, Smith & Buchwald 2002). Patients with FM or MCS have been found to also meet case criteria for CFS/ME (Buchwald, Garrity 1994, Donnay, Ziem 1999, Slotkoff, Radulovic & Clauw 1997). It has also been suggested that fibromyalgia may be a variant of CFS/ME (Buchwald 1996, Slotkoff, Radulovic & Clauw 1997) although there appears to be contradictory evidence that indicates CFS/ME and fibromyalgia may be distinct clinical entities (Robbins, Kirmayer & Hemami 1997).

Jason et al. (2000) found that 15.6% of individuals diagnosed with CFS/ME had coexisting FM and 22.7% of individuals initially diagnosed with FM also had a diagnosis of CFS/ME (Jason, Taylor & Kennedy 2000). This study also found that 14.4% of those diagnosed with CFS/ME also met criteria for Multiple Chemical Sensitivity (MCS). However, different estimates have been produced elsewhere (Buchwald, Garrity 1994, Slotkoff, Radulovic & Clauw 1997).

Despite the various research conducted in this area, none has produced valid explanations for the overlap or significant differences between CFS/ME, FM and MCS. Studies focusing on the relationships between the three syndromes have reported different findings. In a study that excluded major symptom criteria such as fatigue and widespread pain, latent class analysis results showed that CFS/ME and FM had more similarities than differences (Aaron, Buchwald 2001). It is thought that the removal of the major symptoms influenced the outcomes as the results did not reflect those of subsequent studies, which provided validated evidence of the diagnostic distinctions between FM, CFS/ME, somatic depression, somatic anxiety, and IBS (Taylor, Jason & and Schoeny 2001).

Case-definitions and similarities between the CFS/ME, FM and MCS are shown in Table 3.

Table 3 CFS/ME and medically concomitant conditions (Institute of Medicine 2000)

	CFS/ME	FM	MCS
Most common symptoms	Severe fatigue, headaches, post-exertional fatigue, impaired cognition, muscle pain, multi joint pain, sore throat, unrefreshing sleep, sudden onset of symptoms with a flu like illness	Widespread muscle pain and stiffness, tenderness at specified soft tissues sites, fatigue, sleep disturbance, impaired cognition	Fatigue, low energy, inability to concentrate, memory problems, nasal congestion, headache, throat soreness, joint discomfort
Classification criteria	1988 CDC case-definition, revised 1994	1990 American College of Rheumatology	No widely accepted criteria
ICD-10 listing	Yes	Yes	No
Causes	Unknown	Unknown	Unknown
Laboratory test	No pathogenic markers identified	No pathogenic markers identified	No pathogenic markers identified
Biological correlates	HPA dysregulation and other CNS abnormalities, immune activation, physical and cardiovascular de-conditioning	HPA dysregulation, alterations in pain mediators (substance P, dynorphin), growth hormone deficiency	None yet identified
% significant disability	Striking disability in role and social functioning and vitality, 37% unemployed	26.5 % of FM patients report receiving disability payments	43% of MCS patients report disability

Major depressive disorder

The role of major depression in CFS/ME is quite important as studies show that it is probably the most common psychiatric illness coexisting with CFS/ME. As a result, different hypotheses have been postulated on the relationship between both conditions. The 1994 CDC case-definition recognised the need to clarify the role of psychiatric co-morbidities in CFS/ME. Some researchers believe that psychiatric disorders are important risk factors involved in the causation of CFS/ME. However, recent findings indicate that not all CFS/ME patients have psychiatric co-morbidities (Moss-Morris, Petrie 2001).

Further, subsequent research undertaken after the development of the CDC 1994 case-definition disprove the hypothesis that CFS/ME is a manifestation of major depression as suggested by some researchers. DeLuca et al. (1997) demonstrated the differences between CFS/ME patients and patients with depression. He went further and suggested that CFS/ME patients without a history of psychiatric illness were a potential subgroup with the highest probability of finding reproducible biomedical markers (DeLuca et al. 1997).

3.6. Summary

This chapter has examined CFS/ME case-definitions, commonly associated symptoms, evidence for CFS/ME subgroups and co-morbid entities. The current case-definitions for CFS/ME are non-specific and are based on expert opinion rather than derived from data on real CFS/ME patients. The differences in the criteria for the case-definitions demonstrate the divergent views on the nature and scope of CFS/ME. Proposals for addressing some of problems highlighted in the case-definitions include:

(i) Incorporating methods that would allow the provision of data for the performance of a classification system; providing supporting data to link

symptoms to CFS/ME. Some of the current systems incorporate psychiatric co-morbidities e.g. depression as a valid construct in CFS/ME without adequate evidence to support their view;

(ii) Ensuring internal inconsistency between how CFS/ME is defined and required criteria; employing suitable validation methods to aid the development of an epidemiological case-definition;

(iii) Providing clear statements on departures in terminology on critical differences between old and new terms to reduce ambiguity and improve interpretation across definitions.

(iv) Defining subgroups using empiric methods.

Chapter 4: Materials and Methods

4.1. Introduction and statement of problem

This chapter describes in detail the procedures for data collection and analysis, the ethical issues and justification for the methodology as reflected in the four major stages of activities involved in this part of the research. These were the developmental, data collection, panel review and analyses stages.

4.2. Development of the study protocol and methods

This important aspect of the research process defined the aims and objectives of the study and the activities to be undertaken during data collection and the panel review. The activities undertaken included:

- A review of the literature to identify the clinical research case-definitions for CFS/ME in use.
- The development of the study rationale, specific aims and objectives and the study design in terms of the study population, eligibility criteria and statistical methods.
- Preparation of the data collection tool.
- The identification and consideration of the ethical and governance issues relating to the research.
- Piloting of the form.

4.2.1. Study setting and participants

This research was a descriptive epidemiological study set in primary care involving a cross-sectional analysis of general practice data. In most cases, a retrospective review of medical notes was undertaken. The study population consisted of patients registered with a General Practitioner (GP) in the UK with unexplained chronic fatigue of at least six months duration (incident and prevalent cases).

The primary care setting was the best setting for the study as more than 97% of the UK population are registered with a General Practitioner (Royal College of General Practitioners 2004). Individuals with CFS/ME are therefore more likely to present in primary care than any other health care setting in the UK.

Sample size

At the time of research, there were no existing gold standard epidemiological case-definitions for CFS/ME. The study was largely exploratory in nature and there was no suitable data set on which to power the study. The final sample size calculation was based on the discriminant analysis requirement of a minimum of 2 to 3 cases for each variable included in the analyses (Klecka 1980).

Study tools

The questions were based on diagnostic criteria from the CDC 1988 and 1994, the Australian, the Oxford and the Canadian case-definitions (Appendix F). It was not possible to establish the validity of the epidemiological case-definition as there were no biological measures of pathology or etiology (Faraone and Tsuang, 1994). Statistical techniques (described in latter sections of this chapter) were employed in defining a case of CFS/ME—in the absence of a diagnostic gold standard which also involved reliability and validity testing (Institute of Medicine 2000).

One of the reasons for using clinical research case-definitions was to satisfy validity requirements through the inclusion of items of relevance and importance to the study area. These were case-definitions which had been developed specifically for clinical studies or the diagnosis of CFS/ME (content validity).

The final data collection-tool was a 93-item form (Appendix G) consisting:

(i) Symptoms associated with CFS/ME:

- Fatigue symptoms
- Immune symptoms/Infection
- Functional impairment and disruption of normal activity
- Musculoskeletal symptoms
- Visual disturbances
- Psychiatric and mental symptoms
- Perceptual or sensory disturbances
- Neurological and cognitive symptoms

(ii) Medical and psychiatric conditions for exclusion during diagnosis:

- Any active disease process that explained most of the major symptoms of fatigue, sleep disturbance, pain, and cognitive dysfunction. e.g. Addison's disease, Cushing's syndrome, hypo/hyperthyroidism, treatable forms of anaemia, iron, diabetes and cancer.
- Rheumatological disorders e.g. rheumatoid arthritis, lupus, polymyositis and polymyalgia rheumatica.
- Immune disorders e.g. AIDS.
- Neurological disorders e.g. multiple sclerosis, Parkinsonism, myasthenia gravis and vitamin B12 deficiency.
- Infectious diseases e.g. tuberculosis, chronic hepatitis and Lyme disease.
- Primary psychiatric disorders and substance abuse.

(iii) Co-morbid conditions e.g. fibromyalgia syndrome, anxiety disorders, somatoform disorders, non-psychotic or non-melancholic depression, irritable bowel syndrome, premenstrual syndrome and multiple chemical sensitivity disorder.

(iv) Demographics of the individual in relation to age, gender, race, education level, marital status, employment status.

(v) The GP's provisional diagnosis.

(vi) An indication of whether the patient was present or absent during completion of the form.

It was assumed that unless stated on the form or in the GP's provisional diagnosis that patient had been treated and recovered, comorbid conditions e.g. hypothyroidism were not fully resolved and therefore provided an alternative explanation for the symptoms. Other conditions such as anxiety disorder and depressive disorders were also assumed to be present at the onset of illness and were not regarded as a consequence of CFS/ME.

A simple response format was used and participants offered three choices of response: "yes", "no", or "don't know" in order to provide clarity on the specific information within GP records. A 'yes' response indicated that a particular symptom or condition was present and confirmed at onset of the illness unless stated otherwise by the respondent. A 'no' response indicated that the symptom or condition was absent and had been confirmed. The 'don't know' field was specifically included for responses where the respondent was not certain of a symptom after a consideration that the GPs may not have information on all the questionnaire items. This reduced the likelihood for guessing on part of the GPs.

For analytical purposes however, a 'yes' response was an indication of unequivocal evidence that the symptoms existed, otherwise any other response was 'no'.

A Microsoft Access database was then created using the questionnaire format for data input, management and storage.

Ethical and governance issues

The ethical issues associated with the study included:

- Informed consent issues.
- Privacy and confidentiality issues.

Ethical approval for the study was sought and obtained from the South West Multicentre Research Ethics Committee (MREC).

Informed consent

GP information sheets were prepared to inform potential participants of the nature and purpose of the research. Participation was formally invited through consent forms sent to GPs (2 copies) which they were asked to sign to indicate their agreement to participate. Consenting GPs were asked to retain a copy of the consent forms for their records.

Privacy and confidentiality

Care was taken to ensure anonymity and confidentiality by:

(i) Eliminating all personal identifiers from both responders and individuals.

(ii) Assigning study reference numbers to forms completed for each case.

(iii) Retaining consent forms in locked storage separated from the study data.

PCT management approval

All relevant Primary Care Trusts (PCTs) and Local Health Boards (> 200 NHS organisations) in England, Scotland and Wales were notified of the study in line with requirements of the research governance framework.

4.2.2. Pilot study

A small pilot survey was undertaken to:

(i) Obtain participant feedback on instrument clarity

(ii) Determine the length of time it would take to complete the form

(iii) Facilitate data collection and reduce errors once forms were sent to the GPs

(iv) Determine how readily the data could be collected and transferred

(v) Detect difficulties in the data collection and flow procedures

(vi) Detect difficulties in the content of specific questions

(vii) Identify problems with the information collected

Three GP members of the charity *Action for ME* who had shown an interest in the study were informed of the study in writing and asked to complete 1-2 forms each for incident and prevalent cases of unexplained chronic fatigue on their lists of at least 6 months duration.

The feedback from the pilot showed that the form could be completed within 10-15 minutes. There did not appear to be any difficulties in the content or clarity of questions as all check boxes were ticked. Instructions for completing the form were modified to emphasise completion time and return-by date of two weeks to facilitate the identification and follow up of non-responders.

4.2.3. Recruitment of study participants

Application to the Action for ME

The charity *Action for ME* (AfME) was initially approached to help recruit GPs to the study. A total of 50 GPs were identified from the AfME's database but only eight GPs consented to participate in the study.

Application to the General Practice Research Framework (GPRF)

Five months later, following the lack of participation by further GPs from AfME, the study was extended to the Medical Research Council General Practice Research Framework (MRC-GPRF) an organisation of over 1000 general practices throughout the UK involved in epidemiological, primary care and health services research.

4.2.4. Data collection and follow-up

Data collection activities were facilitated by the diligent cooperation and participation of the MRC-GPRF personnel. Study packs consisted of introductory letters from the MRC-GPRF, forms, consent forms, information sheets and reply paid envelopes. These were distributed to six hundred and seventeen MRC-GPRF general practices and non-responders were followed up.

GPs were asked to return the forms in the reply paid envelopes. They were asked to reply if they did not want to participate in the study in order to facilitate the follow up of non-responders. GPs were also informed that they could photocopy forms for additional patients or give the forms to other colleagues with an interest in the area of research. GPs were given a £10 book token for each completed form. Data collection and follow-up was conducted four different times over a period of 11 months.

4.2.5. The panel review

The task of the expert reference group

Seven potential reviewers with special interests, professional expertise and ability to contribute to CFS/ME research were identified from the members of the Chief Medical Officer's CFS/ME Working Group. They were invited to join the expert reference group for the study and asked to assist in the development of the epidemiological case-definition for CFS/ME. Three individuals agreed to join the group and were sent further study details. A fourth reviewer who was a GP with a special interest in CFS/ME research also joined the expert panel. The reviewers had specialist knowledge and skills in the study area and were of academic and medical backgrounds. The main focus of the reviewers was to assign cases to disease and non-disease groups from the data collected during the course of the study. This involved three rounds of reviews which were conducted over a five-month period.

Reviewers were contacted by post, email and telephone having been forewarned of the mode of communication at the time of invitation. Reviewers were assigned an identification number (ID) known only to the researcher. Further, the reviewers were blinded to the GP's diagnoses. Each reviewer received different sets of randomly selected case forms and was asked to make a judgement on the likelihood of a case being CFS/ME (disease group) or not CFS/ME (non-disease group) thereby confirming or disagreeing with the GPs diagnoses.

4.2.6. Scoring the proforma

Forms were rated blindly by the reviewers who also indicated their level of confidence in their ratings on a 5-point scale due to the lack of a gold standard epidemiological case-definition (Appendix K). This accounted for different levels of certainty for the presence or absence of CFS/ME (England et al. 2005). In order to

produce a simple composite score for the reviewers' direct ratings, the 5 point scale for both disease and non-disease groups was combined and converted to 10 resultant scores ranging from 0-9 (Appendix L). All the reviewers rated a specified number of forms for the same cases at the first round. Subsequent rounds involved ratings of individual cases by different reviewers. Where ratings were unclear for any particular case this was sent to another reviewer who had not been involved in the initial review of the case.

4.3. Data processing

4.3.1. Data quality assessment

All data including responses from the reviewers were entered into a Microsoft Access 2003 database. Data cleaning, manipulation and quality checking were undertaken in the Access datasheet view. The internal validity of the data was assessed by manually cross checking the datasheet against every form for accuracy.

4.3.2. Data Management

The data was subsequently exported to an SPSS 14.0 database for analysis using the SPSS query generator. Quality assurance for the transfer activity between databases included visual inspection of printout of the Microsoft Access tables and comparison with the SPSS data. In addition the SPSS database was checked for errors and cleaned electronically by producing frequencies of responses to each item and looking for invalid responses before analyzing the data.

The SPSS programme automatically screened variables for blank entries to determine the proportion of missing data in each variable providing an indication of completeness i.e. proportion of data cells in each variable that contained valid cell values. When working with the data, fields with 'yes' and 'no' values were coded 0 and 1

respectively. Missing values were coded as ‘999’. Don’t know responses were coded as 0 or 1 during the analyses and used to check the sensitivity of the results. There was a possibility that GPs did not have the specialist knowledge to the answer some questions and had selected the ‘don’t know’ option or because the information was not available rather than unwillingness’ to provide the information.

4.4. Analytical approach to developing the case-definition

The main analytical methods employed were as follows:

(i) Computation of reliability statistics for the rating process

(ii) Conversion of initial ratings to resultant scores

(iii) Exploratory analyses to assess the structure of the data

(iv) Multivariate analytical methods to compute the discriminant function in discriminant analysis.

The dependent variable was the reviewers’ overall score (which determined classification group), while the independent variables were the symptom criteria. Due to the fact that symptoms vary from case to case, the questionnaire items representing the variable symptoms were organised by summary values e.g. yes or no, or more subtle measures where possible e.g. immune, neurological, and miscellaneous groups (Appendix M). Other grouped variables included co-morbid conditions, current level and total duration of fatigue, current level of functional impairment and type of fatigue onset (Whistler et al. 2003). This approach enabled the stratification of cases for the analyses.

4.4.1. Definition of case

The criteria used to define a given record as a case of CFS/ME for the purpose of the following analysis was based on the mean score of the reviewers. This formed the gold standard against which other CFS/ME classification criteria used in this study were assessed. Four (4) threshold levels of diagnostic certainty were assessed at each stage of the analysis and used to construct 4 sets of case-definition algorithms or models which could be rank ordered by estimated ordinal likelihood of disease(England et al. 2005).

4.4.2. Reliability

Reliability refers to "the extent to which a measurement procedure yields the same results on repeated trials (either at different time points or across different raters)" (Institute of Medicine 2000). The reviewers' ratings and confidence scores were combined to produce a single measure (Appendix L) and Kappa was computed to assess inter-reviewer reliability. The degree of variability in the scores for the individual cases was assessed by calculating descriptive statistics and producing graphs of the reviewers' scores.

4.4.3. Discriminant analysis

In the study, two methods of discrimination were employed which were based on classical discriminant analysis and the sum of binary variables. Discriminant analysis (DA) is "a term that covers a large number of techniques for the analysis of multivariate data, that have in common the aim to assess whether or not a set of variables distinguish or discriminate between two (or more) groups of individuals" (Everitt 1996).

The classical DA is a linear method based on Bayesian analysis. The single combination of variables derived using DA that best distinguishes between different groups is called the *discriminant function*.

In discriminant analysis, the groups are determined beforehand and the objective is to determine the linear combination of independent variables which best discriminates among these groups. For the current study, the value returned by the 'linear combination of variables', could assign a certain proportion of cases to the correct group (as determined by the gold standard/reviewers) thereby distinguishing between the two main groups in the study i.e. the CFS/ME and non-CFS/ME (CF) groups.

Discriminant analysis has two main steps:

(1) An F test (Wilks' lambda) used to test if the discriminant model as a whole was significant and,

(2) Group means test as a result of a significant F test. The individual independent variables were assessed to see which of the variables differed significantly in mean by group and these were used to classify the dependent variable (Everitt 1996).

The discriminant function also called a *canonical root*, is a latent variable created as a linear combination of discriminating (independent) variables, such that $Z = W_1X_1 + W_2X_2 + ... + W_nX_n + c$, where the W's are discriminant coefficients, the X's are discriminating variables, and c is a constant. The discriminant coefficients (W's) serve to maximize the distance between means of the dependent variable.

The equation used to predict the group of a new case (Kirkwood 1988) was thus $Z = W_1X_1 + W_2X_2 + W_3X_3 + \ldots + W_nX_n$

where:

- **Z** = the discriminant score, also called the DA score. This is the value resulting from applying a discriminant function formula to the data for a given case for standardized data. If the discriminant score of the function was less than or equal to the cut off, the case was classed as 0, or if above the cut off, it was classed as 1. When group sizes were equal, the assigned cut off was the mean of the two centroids (for a two-group DA). If the groups were unequal, the cut off was the weighted mean.

- **W_i** = Discriminant coefficient (weight) for variables. The discriminant function coefficients are partial coefficients, reflecting the unique contribution of each variable to the classification of the dependent variable. Unstandardised discriminant coefficients are used in the formula for making the classifications in DA. The constant plus the sum of products of the unstandardised coefficients with the observations yields the discriminant scores. The standardized discriminant coefficients are used to assess the relative classifying importance of the independent variables. Addition or deletion of variables in the model can change the discriminant coefficients markedly. Since these are partial coefficients, only the unique explanation of each independent is being compared, not considering any shared explanation.

- X_i = independent variable i

Functions at group centroids are the mean discriminant scores for each of the dependent variable categories for each of the discriminant functions DA. Two groups of centroids which were the mean values of the discriminant score Z were produced, one for each of the two groups. These indicated the most typical location of any individual from a particular group and a comparison of the group centroids indicated how far apart the groups were. Well apart means show the discriminant function is clearly discriminating. The closer the means, the more errors of classification there likely will be. (Everitt 1996).

Other aspects of the discriminant analysis procedure were as follows-

(I) Setting the objectives

Primary objectives for the DA included:

a. Identifying and minimising the number of errors in prediction;

b. Determining whether statistically significant differences existed between the average score profiles on a set of variables for the two groups;

c. Assessing which of the independent variables accounted the most for the differences in the average score profiles of the groups;

d. Establishing procedures for classifying cases and non-cases of CFS/ME on the basis of their own scores from a set of independent variables;

e. Ascertaining the number and composition of the dimensions of discrimination between cases and non-cases from the set of independent variables.

(II) Planning the analysis

a. The dependent and independent variables were selected:

- Independent variables: These are the discriminating (predictor) variables.
- The dependent variable: This is the object of classification efforts, also known as the criterion variable, or the *grouping variable* in SPSS.

The dependent variable was identified as the confirmation of the diagnosis of CFS/ME (categorical). This was mutually exclusive and exhaustive i.e. no person fell into both categories of CFS/ME and non-CFS/ME. Further, it was not possible to choose any other option outside the context of the study. The independent variables were identified as the symptom criteria which were metric i.e. yes or no (0/1).

With two categories of the dependent variable, DA estimated a discriminant function, representing a different dimension of discrimination. The mean scores of each group were examined to see if one of the variables discriminated well among all the groups. DA produced a weighted combination of the criteria which predicted a case of CFS/ME and identified the characteristics that differentiated cases from non-cases. DA also distinguished CFS/ME cases from other forms of chronic fatigue i.e. FMS, IBS, PMS and MCS.

b. Canonical discriminant functions were computed. The significant aspects related to this process include comparison of distances between group means, the number of discriminant functions and eigenvalues. However in this study only the eigenvalues are assessed due to the fact that not more than two groups and one discriminant function are involved in the analysis.

The eigenvalue is also called the characteristic root of the discriminant function. It reflects the ratio of importance of the dimensions which classify cases of the dependent variable. Eigenvalues which were greater than 1 were taken to be significant. In this study which was a two-group DA, there was one discriminant function and one eigenvalue for each for each discriminant function group. The eigenvalue assessed relative importance of the function by reflecting the percentage of variance explained in the dependent variable, cumulating to 100% for the function (Garson 1996, 2006).

c. Tests of significance: Wilks' lambda was used to test the significance of the discriminant function (its significance level) as a whole. The larger the lambda, the more likely it was significant. A significant lambda meant one could reject the null hypothesis that the two groups had the same mean discriminant function scores and conclude the model was discriminating.

d. Fisher's linear discriminant functions: This is the classical method of discriminant classification used to calculate one set of discriminant function coefficients for each dependent category to make the classifications. The Fisher coefficients were used to compute a discriminant score for each dimension and each case was classified to the group generating the highest score.

e. Stepwise DA: Stepwise procedures selected the most correlated independent variable first, then removed the variance in the dependent variable, followed by select ion of the second independent variable which most correlated with the remaining variance in the dependent variable, and so on until selection of an additional independent variable did not increase the R-squared value by a significant amount

(usually significance=.05). In this study, forward (adding variables) stepwise procedures were selected in SPSS.

f. Classification Matrix: As binary predictive models were considered, the overall accuracy was assessed by constructing a classification matrix. This comprised: true positive, true negative, false positive and false negative. These were then used to calculate various performance measures that described each model's ability to discriminate between CFS/ME and non-CFS/ME (CF group). The main measures considered included sensitivity (proportion of actual present correctly predicted or classified), and specificity (proportion of actual absent correctly classified).

The table rows in the matrix were the observed categories of the dependent and the columns were the predicted categories of the dependents. A perfect prediction is displayed by all cases lying on the diagonal. The percentage of cases on the diagonal is the percentage of correct classifications known as the hit ratio or overall accuracy.

- *Expected overall accuracy*. The overall accuracy was compared to the percentage that would have been correctly classified by chance alone.
- *Cross-validation*. Leave-one-out classification in SPSS was used as a form of cross-validation of the classification table. Each case was classified using a discriminant function based on all cases except the given case.

Measures of association were computed by the crosstabs procedure in SPSS by saving the predicted group membership for all cases

Model assessment

The statistical models derived from the DA were compared on the basis of their classification accuracies and receiver-operating characteristic (ROC) curves. The classification accuracy was appropriate for the assessment because prediction of CFS/ME cases was of primary interest. The ROC plot gauged how well the "receiver" (in this case, each model) assigned cases to the CFS/ME and non CFS/ME groups and

was obtained by plotting all sensitivity values on the *y*-axis against their equivalent (1−specificity) (false positive fraction) values on the *x*-axis.

The estimated area under the curve (AUC) of the resulting plot provided a measure of overall accuracy based on threshold values which were then translated as the probability that the model would correctly distinguish between two cases (DeLeo 1993). Unlike threshold-dependent accuracy measures, AUC is also independent of prevalence thus making it particularly appropriate for this study. While ROC curves were the main method of model accuracy assessment used here i.e. during the discriminant analysis, they did not fully replace threshold-dependent measures. A further assessment of the independent variables selected by the DA method for each model was conducted to elicit potential subgroups through defined symptom clusters and symptom severity.

During the discrimination involving the unweighted sum of binary variables, an optimal threshold for each model was selected near the point that all three lines (sensitivity, specificity, total accuracy) crossed, with an emphasis on ensuring sensitivity was relatively high. This method avoided a limitation of the classical discriminant analysis by not using classification accuracy as the primary measure of model accuracy and it also considered the other aspects of model complexity i.e. the number of parameters required for discrimination. The sum of binary variables is discussed further in subsequent chapters.

4.4.4. Sensitivity analyses of previous research case-definitions

Sensitivity analysis is defined as, "a test of the stability of the conclusion of an analysis over a range of probability estimates, value judgments and structural assumptions." The main purpose for conducting the sensitivity analysis was to assess the impact of previous case-definitions on ascertainment i.e. to determine the proportion

of CFS/ME cases who met criteria for clinical research definitions used in previous epidemiological studies.

Case ascertainment or identification within the context of the study involved identifying all cases of CFS/ME firstly through the reviewers, and then secondly on basis of other existing research case-definitions. Completeness of case ascertainment is defined as the extent to which all the cases are determined and is an indication of how well current research definitions perform when compared to the study gold standard. This provided a framework for comparing or interpreting previous work based on the clinical research definitions used in this study.

4.4.5. Review of basis of diagnosis

A review of the clinical diagnosis of CFS/ME in general practice was undertaken in order to determine the extent of GPs knowledge of CFS/ME by assessing the accuracy of their diagnoses with the current clinical-case definition for CFS/ME and specialist opinion. The agreement between the GPs diagnoses, clinical case-definitions and the reviewers' opinions were assessed using kappa statistics. The accuracy of diagnosis was also determined.

Flow chart of research process

For the development of an epidemiological case-definition for CFS/ME, the following flowchart outlines the steps that were followed.

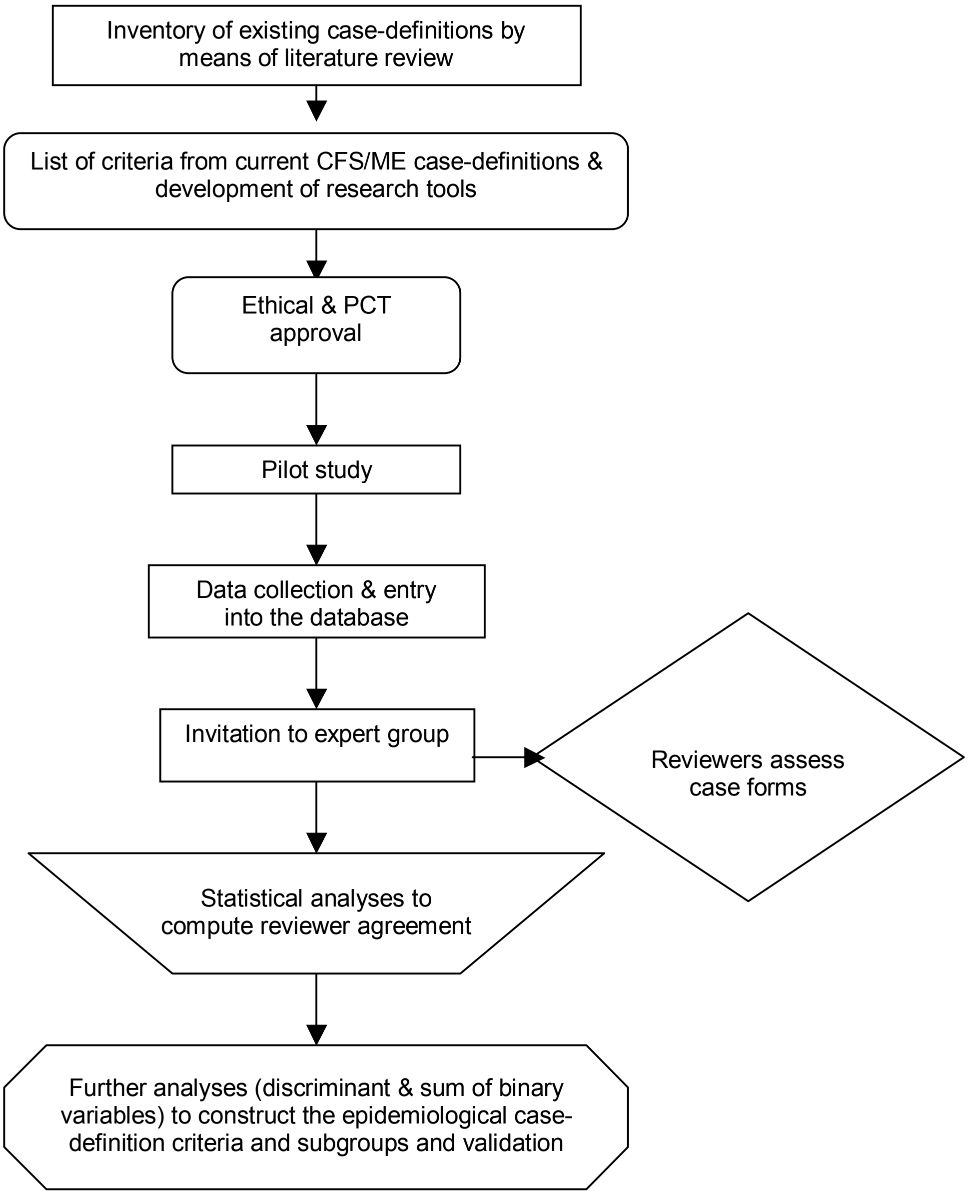


Figure 1 Flow chart of the research process

Chapter 5: Analysis and Results

5.1 Introduction

The analyses presented in this results section relate to the data collected from the forms included in Appendix G. The data for the study was provided by GPs completing proformas for primary care patients between September 2004 and December 2005. The purpose of the study was primarily to identify the parameters that discriminate between individuals with CFS/ME (CFS/ME cases) and those without with other chronic fatigue illnesses (non-CFS/ME comparison group).

617 general practices were contacted. 70 GPs consented to participate in the study and completed proformas for 162 cases and controls. The participating GPs were located in the following regions: London, South East England (Kent, Surrey and Hampshire), West Midlands (Birmingham, Staffordshire and Herefordshire), South West England (Bristol, Devon, Dorset, Gloucestershire and Wiltshire), North West England (Cheshire, Merseyside, Greater Manchester and Cumbria), North East England (County Durham and Middlesbrough), East Midlands (Nottingham, Leicestershire and Northampton), Yorkshire (Bradford and Lincoln), Eastern England (Cambridge, Norfolk, Bedford and Suffolk), Wales (Aberystwyth, Gwynedd, Powys and Flintshire) and Scotland (Edinburgh, East Lothian, Perth and Wick).

20 practices formally declined to participate in the study returning uncompleted questionnaires as requested. Reasons cited for non-participation included lack of time and non-familiarity with the subject area. Five (5) practices stated that they did not have patients who met the inclusion criteria.

158 forms were completed from medical records and four completed during consultations. Data collection formally ended on the 31st of January 2006. The data recorded were stored in a database and a statistical program (SPSS 14.0) was used for the subsequent analyses.

5.2 Case identification and reliability measures

Case assignment was made by four (4) reviewers on the basis of the information provided in completed proformas in absence of biological markers. The four reviewers did not meet collectively to discuss the case identification criteria or definitions. Each reviewer assessed the forms with his/her own experience and understanding of CFS/ME. A total of 154 forms received by the 31st of January 2006 were rated independently by the reviewers. The remaining 8 forms received after the 31st of January were not included in the review though they were included in the statistical analysis. The distribution of the forms to the reviewers is shown in Table 4.

Table 4 Distribution of reviewed forms

Reviewers	Number of forms assessed
Reviewer 1	104
Reviewer 2	103
Reviewer 3	77
Reviewer 4	79

The reviewers were blind to the GPs' diagnoses and evaluated each case on an ordinal scale (i.e. 'very low confidence CFS/ME to very high confidence CFS/ME' or 'very low confidence non-CFS/ME to very high confidence non-CFS/ME') as shown in (Appendix K). The 5 point scale for disease and non-disease groups were combined and translated to scores of 0-9 (Appendix L) on a 10-point scale. The distribution of the scores is shown in figure 2.

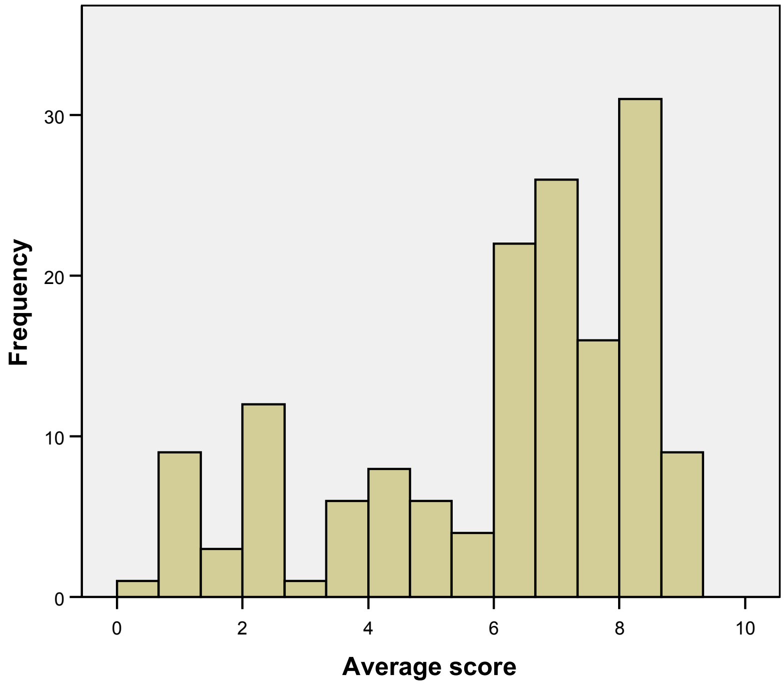


Figure 2 Distribution of the reviewers average scores

5.2.1. Reliability

Inter-observer agreement in the assessment of disease status between the four reviewers was assessed by using the percentage agreement and kappa. The kappa values assigned less weight to agreement as rating scores between reviewers were further apart on the ordinal scale (Cohen 1968). The null hypothesis of no agreement between paired reviewers was tested and the associated p-values were computed.

Firstly, the cases were reviewed independently for the presence or absence of CFS/ME and rating scores were derived. These were used to classify all the cases by computing the arithmetic mean of the scores of the 4 reviewers (the mean rating score). Secondly, all the cases with mean scores ranging from 5-9 were placed in CFS/ME subcategories (subsets) and those with mean scores less than 5 were regarded as the

non-CFS/ME comparison group. Therefore cases were judged to be CFS/ME if they were above or equal to the cut-points of five (≥5 points), six (6), seven (7) and eight (8).

Cross tabulations were produced by pairing the reviewers and comparing their assessment of cases by way of the contingency table. All kappa (κ) values were interpreted on the basis of data in the literature (Cohen 1968, Landis 1977). A κ value of less than 0.20 indicated poor agreement; 0.21– 0.40, fair agreement; 0.41– 0.60, moderate agreement; 0.61– 0.80, good agreement; and 0.81– 1.00, excellent agreement. The κ values derived from the mean scores are shown in Table 5.

Table 5 Kappa values for the four reviewers

Scale	Number of cases	Concordance %	κ	Approx Sig.
reviewer 1 vs. reviewer 2	53	79.2	.350	.010
reviewer 1 vs. reviewer 3	54	77.8	.469	.000
reviewer 1 vs. reviewer 4	44	86.4	.660	.000
reviewer 2 vs. reviewer 3	47	63.8	.216	.128
reviewer 2 vs. reviewer 4	47	78.7	.315	.029
reviewer 3 vs. reviewer 4	35	86.1	.625	.000
Average		78.7	***0.439***	

Overall, the agreement among reviewers was fair to moderate (range 0.216 – 0.660, average κ, 0.439). The κ values tended to be higher between reviewers 1 and 4 and reviewers 3 and 4. The comparison of percentage of agreement between the four reviewers showed high levels of concordance. The lowest concordance occurred between reviewers 2 and 3. Average concordance was 78.7%.

Judging by the κ value for inter observer agreement not due to chance, moderate agreement was recorded between reviewers 1 and 3 and reviewers 2 and 4. Good agreement was recorded between reviewers 1 and 4 and reviewers 3 and 4. In these instances, the null hypothesis of no agreement between two observers was rejected. Conversely although observed agreement between reviewers 2 and 3 was moderate, the κ value was non-significant.

5.2.2. Classification cut-off scores (threshold levels)

The classification cut-off score i.e. the average score at which a case was classified as CFS/ME was set at 4 different thresholds to allow further sensitivity analyses of the results (refer to Appendix L for conversion tables). The four classification cut-off scores were thus ratings equal to or greater than, 5, 6, 7 and 8. Subsequent analyses are based on these four ratings.

Table 6 displays the distribution of CFS/ME cases and controls on the basis of the four classification cut-off scores.

Table 6 Total sample of cases (CFS/ME) and controls (non-CFS/ME) by classification cut off score (n=162)

Cut-off 8 (Subset D)			**Cut-off 6 (Subset B)**		
	N	%		N	%
CFS/ME	54	33.3	CFS/ME	106	65.4
non-CFS/ME	99	61.1	non-CFS/ME	47	29
Sub-total	153	94.4	Sub-total	153	94.4
Missing (unrated)	9	5.6	Missing (unrated)	9	5.6
Total	162	100	Total	162	100
Cut-off 7 (Subset C)			**Cut-off 5 (Subset A)**		
	N	%		N	%
CFS/ME	84	51.9	CFS/ME	119	73.5
non-CFS/ME	69	42.6	non-CFS/ME	34	20.9
Sub-total	153	94.4	Sub-total	153	94.4
Missing (unrated)	9	5.6	Missing (unrated)	9	5.6
Total	162	100	Total	162	100

The distribution of CFS/ME cases and non-CFS/ME comparison group for scores 5 or greater was 73.5% and 20.9% respectively, for scores of 6 or greater was 65.4% and 29% respectively, for scores of 7 or greater was 51.9% and 42.6% respectively and for scores of 8 or greater was 33.3% and 61.1% respectively. The missing data in the table were cases not assigned to groups by the reviewers. As expected, the proportion of CFS/ME cases decreased with higher classification cut-off scores.

5.3. *Sample description*

5.3.1. Socio-demographic characteristics

The total sample size for the study was 162. The description of the socio-demographic characteristics of the sample was based on self-reported values. These were key characteristics which enabled the checking of the balance between the CFS/ME cases and non-CFS/ME comparison groups within the study population and generalisability of the results.

Univariate statistical analysis was conducted to assess the association between the socio-demographic characteristics of the study sample and the assigned disease status. The variables considered in this analysis were age, professional qualifications, education, employment, race and gender.

The results of the analysis (excluding missing values) are shown in Table 7. Results are reported with a significance level of $p < .05$. As can be seen in Table 7, the distribution of the sample (162 in total) by age groups showed that majority of the sample was in the age range 31-50 (48.7%). Only 6.7% were below the age of 20. 42.5% were reported as having professional qualifications and 57.5% reported as not having any qualifications. 76.3% attained educational qualifications beyond the minimum school leaving age. When assessing employment status, the majority of the sample (excludes missing data) 63 (39.5%) were reported as unemployed. 58 (42.1%) of these were unemployed for health reasons and this was almost equal to those in part-time or whole time employment (39.1%). The racial background of the sample was predominantly white (95.4%). Other racial backgrounds were Asian (3.3%) or mixed (1.3%). Females accounted for over two thirds (69.2%) of the sample size whilst 30.8% were male.

The results of the analysis shown in Table 7 also reflect that none of these variables were strongly associated with the disease status and they did not contribute to the probability of a case being ascertained. As a result, they were omitted from the final multivariate discriminant models that assessed the predictors of CFS/ME.

Table 7 Socio-demographic profile of the study sample and association with CFS/ME cases and non-CFS/ME comparison group (missing values excluded)

		cut-off score 5				**cut-off score 6**				**cut-off score 7**				**cut-off score 8**			
		CFS/ME		Non-CFS/ME		CFS/ME		Non-CFS/ME		CFS/ME		Non-CFS/ME		CFS/ME		Non-CFS/ME	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Age-group	11-20	8	5.3	2	1.3	8	5.3	2	1.3	7	4.7	3	2.0	4	2.7	6	4.0
	21-30	21	14.0	2	1.3	20	13.3	3	2.0	16	10.7	7	4.7	12	8.0	11	7.3
	31-40	27	18.0	8	5.3	24	16.0	11	7.3	21	14.0	14	9.3	14	9.3	21	14.0
	41-50	28	18.7	10	6.7	23	15.3	15	10.0	18	12.0	20	13.3	10	6.7	28	18.7
	51-60	21	14.0	8	5.3	19	12.7	10	6.7	14	9.3	15	10.0	10	6.7	19	12.7
	61-70	8	5.3	3	2.0	7	4.7	4	2.7	5	3.3	6	4.0	3	2.0	8	5.3
	>70	2	1.3	2	1.3	2	1.3	2	1.3	2	1.3	2	1.3	1	0.7	3	2.0
Total		115	76.7	35	23.3	103	68.7	47	31.3	83	55.3	67	44.7	54	36.0	96	64.0
p-values		*0.545*				*0.395*				*0.531*				*0.534*			
Profess-ional qualifications	no	50	44.2	15	13.3	47	41.6	18	15.9	40	35.4	25	22.1	24	21.2	41	36.3
	yes	38	33.6	10	8.8	34	30.1	14	12.4	27	23.9	21	18.6	20	17.7	28	24.8
Total		88	77.9	25	22.1	81	71.7	32	28.3	67	59.3	46	40.7	44	38.9	69	61.1
p-values		*0.776*				*0.863*				*0.572*				*0.609*			
Education	no	15	14.9	9	8.9	14	13.9	10	9.9	12	11.9	12	11.9	8	7.9	16	15.8
	yes	63	62.4	14	13.9	56	55.4	21	20.8	46	45.5	31	30.7	30	29.7	47	46.5
Total		78	77.2	23	22.8	70	69.3	31	30.7	58	57.4	43	42.6	38	37.6	63	62.4
p-values		*0.049*				*0.182*				*0.399*				*0.619*			
Employ-ment status	Unemployed due to other reasons	4	2.9	1	0.7	4	2.9	1	0.7	3	2.2	2	1.4	2	1.4	3	2.2
	employed	38	27.5	16	11.6	34	24.6	20	14.5	29	21.0	25	18.1	18	13.0	36	26.1
	unemployed due to health	43	31.2	15	10.9	37	26.8	21	15.2	30	21.7	28	20.3	21	15.2	37	26.8
	never worked	3	2.2	0	0.0	3	2.2	0	0.0	2	1.4	1	0.7	1	0.7	2	1.4
	other	1	0.7	0	0.0	1	0.7	0	0.0	1	0.7	0	0.0	0	0.0	1	0.7
	retired	14	10.1	3	2.2	14	10.1	3	2.2	11	8.0	6	4.3	5	3.6	12	8.7
Total		103	74.6	35	25.4	93	67.4	45	32.6	76	55.1	62	44.9	47	34.1	91	65.9
p-values		*0.777*				*0.434*				*0.853*				*0.971*			
race	Asian	4	2.7	1	0.7	4	2.7	1	0.7	3	2.0	2	1.3	3	2.0	2	1.3
	mixed	2	1.3	0	0.0	2	1.3	0	0.0	2	1.3	0	0.0	2	1.3	0	0.0
	white	109	72.7	34	22.7	97	64.7	46	30.7	78	52.0	65	43.3	48	32.0	95	63.3
Total		115	76.7	35	23.3	103	68.7	47	31.3	83	55.3	67	44.7	53	35.3	97	64.7
p-values		*0.721*				*0.533*				*0.429*				*0.075*			
gender	female	80	54.8	21	14.4	72	49.3	29	19.9	58	39.7	43	29.5	39	26.7	62	42.5
	male	32	21.9	13	8.9	28	19.2	17	11.6	23	15.8	22	15.1	13	8.9	32	21.9
Total		112	76.7	34	23.3	100	68.5	46	31.5	81	55.5	65	44.5	52	35.6	94	64.4
p-values		*0.285*				*0.276*				*0.478*				*0.257*			

No major differences between the socio-demographic characteristics of the CFS/ME cases and non-CFS/ME comparison groups.

5.3.2. Clinical features of the study sample

Clinical signs and symptoms were assessed on the basis of being either reported or not reported. As the cut-off score for CFS/ME ranged from 5-8, the frequencies were calculated on the basis that cases with scores not less than 5 were CFS/ME and cases with scores below 5 belonged to the non-CFS/ME group. This enabled the description of the clinical features of all suspected CFS/ME cases.

Table 8 displays the clinical characteristics of the study sample which includes comorbid conditions and exclusionary diagnoses. The most prevalent reported symptoms were significant disruption of usual activities and severe disabling fatigue affecting physical and mental functioning. The most prevalent reported psychiatric conditions were depression and anxiety disorder. The most prevalent reported comorbid conditions were irritable bowel syndrome and fibromyalgia syndrome.

The least prevalent reported conditions occurred in less than 4% of the study population and thus have little diagnostic value in defining a case of CFS/ME. These included:

- Endocrine disorders: diabetes mellitus, Hashimoto's disease, hyperthyroidism Addison's disease, Cushing's Syndrome
- Neurological disorders, dementia
- Psychiatric disorders such as schizophrenia, delusional disorders, bipolar disorder, melancholic or psychotic depression, psychosis
- Cancer
- Rheumatological disorders
- Substance abuse
- Other diseases e.g. infectious diseases- HIV, chronic or sub acute bacterial disease, fungal disease, parasitic disease
- Upper airway resistance syndrome
- Organic brain disease
- Obstructive or central sleep apnea
- Iron overload syndrome

For the full descriptions of the variables, refer to Appendix G.

Table 8a Clinical characteristics of the study sample (based on data-set A- see Appendix O for detailed analyses)

Clinical characteristics	**CFS/ME**		**Non-CFS/ME**		**Total***	
Signs and symptoms of CFS/ME	N(119)	%	N(34)	%	N(162)	%
Significant disruption of usual activities	112	94.1	33	97.1	145	89.5
Severe disabling fatigue affecting physical and mental functioning	109	91.6	26	76.5	135	83.3
A reduction in activity to less than 50% of the patient's premorbid activity	104	87.4	20	58.8	124	76.5
Mental fatigue	101	84.9	32	94.1	133	82.1
Substantial functional impairment	100	84.0	25	73.5	125	77.2
Functional impairment described as disabling	100	84.0	28	82.4	128	79.0
Prolonged (24 hours or greater) generalised fatigue from levels of exercise easily tolerated in the premorbid state	100	84.0	26	76.5	126	77.8
Muscle pain, multi-joint pain without swelling or redness	100	84.0	21	61.8	121	74.7
Debilitating fatigue not relieved by bed rest	95	79.8	28	82.4	123	75.9
Post-exertional malaise lasting more than 24 hours	93	78.2	21	61.8	114	70.4
Inability to concentrate	90	75.6	26	76.5	116	71.6
Muscle discomfort	90	75.6	18	52.9	108	66.7
Sleep disturbance	90	75.6	27	79.4	117	72.2
Myalgia	87	73.1	22	64.7	109	67.3
Unexplained generalized muscle weakness	81	68.1	18	52.9	99	61.1
Difficulty thinking	80	67.2	20	58.8	100	61.7
Mood disturbance	77	64.7	23	67.6	100	61.7
Forgetfulness	65	54.6	19	55.9	84	51.9
Presence of cognitive or neuropsychiatric symptoms	63	52.9	20	58.8	83	51.2
Substantial impairment in short-term memory or concentration	61	51.3	15	44.1	76	46.9
Generalised headaches (type, severity, or pattern different from premorbid state)	56	47.1	14	41.2	70	43.2
Excessive irritability	51	42.9	13	38.2	64	39.5
Mild fever or chills	49	41.2	9	26.5	58	35.8
Migratory arthralgia without joint swelling or redness	45	37.8	11	32.4	56	34.6
New onset of short term memory impairment	43	36.1	12	35.3	55	34.0
Hypersensitivity to noise	41	34.5	8	23.5	49	30.2
Description of the main symptom complex as initially developing over a few hours to a few days	39	32.8	13	38.2	52	32.1
Intolerance of extremes of heat and cold	37	31.1	12	35.3	49	30.2
Sore throat	34	28.6	6	17.6	40	24.7
Infection at onset or presentation corroborated by laboratory evidence	33	27.7	5	14.7	38	23.5
Perceptual or sensory disturbances	28	23.5	7	20.6	35	21.6
Loss of thermostatic ability or other neuroendocrine manifestation	27	22.7	8	23.5	35	21.6
Painful cervical or axillary lymph nodes	24	20.2	3	8.8	27	16.7
Confusion	23	19.3	6	17.6	29	17.9
Ataxia	23	19.3	6	17.6	29	17.9
New sensitivities to food, medications and/or chemicals	21	17.6	8	23.5	29	17.9
Orthostatic intolerance/autonomic manifestation	20	16.8	3	8.8	23	14.2
Photophobia	19	16.0	4	11.8	23	14.2
Swollen lymph nodes	19	16.0	1	2.9	20	12.3
Transient visual scotomata	7	5.9	1	2.9	8	4.9

Table 8b Clinical characteristics of the study sample (co morbid conditions and overlapping syndromes)

Clinical characteristics	**CFS/ME**		**Non-CFS/ME**		**Total***	
Comorbid conditions and overlapping syndromes	N(119)	%	N(34)	%	N(162)	%
Depression (primary)	65	54.6	27	79.4	92	56.8
Irritable Bowel Syndrome	23	19.3	10	29.4	33	20.4
Migraine	23	19.3	3	8.8	26	16.0
Fibromyalgia Syndrome (FMS)	22	18.5	10	29.4	32	19.8
Anxiety disorder	16	13.4	17	50.0	33	20.4
Premenstrual Syndrome	15	12.6	3	8.8	18	11.1
Irritable Bladder Syndrome	6	5.0	2	5.9	8	4.9
Raynaud's Phenomenon	5	4.2	3	8.8	8	4.9
Temporomandibular Joint Syndrome (TMJ)	4	3.4	0	0.0	4	2.5
Sicca Syndrome	4	3.4	2	5.9	6	3.7
Multiple Chemical Sensitivity	4	3.4	5	14.7	9	5.6
Interstitial Cystitis	3	2.5	1	2.9	4	2.5

Table 8c Clinical characteristics of the study sample possible alternate explanations (exclusionary conditions)

Clinical characteristics	**CFS/ME**		**Non-CFS/ME**		**Total***	
Possible alternate explanations (exclusionary conditions)	*N*	%	*N*	%	*N*	%
Major depressive disorder including endogenous depression	29	24.4	18	52.9	47	29.0
Hypothyroidism	8	6.7	6	17.6	14	8.6
Hyperventilation syndrome	5	4.2	2	5.9	7	4.3
Eating disorder	2	1.7	5	14.7	7	4.3
Myofascial Pain Syndrome (MPS)	2	1.7	2	5.9	4	2.5
Hashimoto's Disease	1	0.8	1	2.9	2	1.2
Cancer	1	0.8	2	5.9	3	1.9
Obstructive or central sleep apnea	1	0.8	0	0.0	1	0.6
Other infectious diseases e.g. HIV infection	1	0.8	1	2.9	2	1.2
Psychosis	1	0.8	1	2.9	2	1.2
Delusional disorders	1	0.8	2	5.9	3	1.9
Neurological disorders e.g. multiple sclerosis (MS)	1	0.8	1	2.9	2	1.2
Upper airway resistance syndrome	0	0.0	1	2.9	1	0.6
Parasitic disease e.g. toxoplasmosis	0	0.0	1	2.9	1	0.6
Bipolar disorder	0	0.0	2	5.9	2	1.2
Substance abuse	0	0.0	2	5.9	2	1.2
Melancholic or psychotic depression	0	0.0	2	5.9	2	1.2
Organic brain disease	0	0.0	1	2.9	1	0.6

** Excludes missing data*

5.4. Analyses

Because of the limitations imposed by the relatively small sample size, a three-stage approach was required to analyse data.

- Firstly univariate analyses using chi square (χ^2) statistics was used to identify possible variables that were associated with CFS/ME status.
- Secondly exploratory analysis using the sum of the binary variables (SBV) was undertaken to distinguish between CFS/ME cases and the non-CFS/ME comparison group.
- Thirdly classical discriminant analysis was performed on selected variables to identify the predictors of CFS/ME that would form the mandatory criteria for defining a case.

The results of the classical discriminant and SBV analyses were then compared and used to construct the CFS/ME case-definition algorithms comprising mandatory and supportive criteria.

5.4.1. Univariate Analysis

Description of commonly occurring features in CFS/ME cases.

The highly prevalent features in CFS/ME cases which did not occur so frequently in the non-CFS/ME comparison group were identified from the results of the univariate analysis. This aided in the selection of the relevant features that are more common and significantly associated with CFS/ME and the non-CFS/ME comparison group. It also prevented the selection of the features which appeared to demonstrate a significant relationship but was not common with either the CFS/ME or non-CFS/ME group.

The criterion for describing and selecting the features was a significant association at a minimum of 75% of the CFS/ME cases. This was applied at the four

different cut-off points or thresholds. For reporting purposes these cut-off points are referred to as 'levels' in this section i.e. cut off 5 is referred to as level 1, cut off 6 is level 2, cut off 7 is level 3 and cut off 8 is level 4.

For the CFS/ME group, a minimum of ten variables demonstrated a statistically significant relationship (p<0.05) in at least 75% of cases only. These included:

1. Severe disabling fatigue affecting physical and mental functioning.

At level 1, there was a "yes" response in 94.9% of the CFS/ME cases but only a "yes" in 75.0% of the non-CFS/ME comparison group. The imbalance was a statistically significant effect (p = 0.001, two-sided). The p-value for this contrast was the p-value given in the chi-square test of association between "severe disabling fatigue affecting physical and mental functioning (yes/no)" and case-definition (CFS/ME, or non-CFS/ME). Results were also statistically significant at level 2 (CFS/ME percentage 95.2% versus non-CFS/ME percentage 79.5%, p = 0.003, two-sided) and at a level 3 (CFS/ME percentage 96.4% versus non-CFS/ME percentage 82.8%, p < 0.005, two-sided). The results at level 4 were not statistically significant.

2. Post exertional malaise

a. Level 1 (93.1% versus 71.4%, p = 0.002, two-sided)

b. Level 2 (93.3%, versus 76.9%, p = 0.008, two-sided)

c. Level 3 (94.7%, versus 79.6%, p = 0.009 two-sided)

d. Level 4 (97.9% versus 82.7%, p = 0.009, two-sided).

3. A reduction in activity to less than 50% of the patient's premorbid activity

a. Level 1 (93.8% versus 66.7%, p < 0.000, two-sided)

b. Level 2 (93.2% versus 75.0%, p = 0.003, two-sided)

c. Level 3 (93.9% versus 80.7%, p = 0.016, two-sided)

d. Level 4 (98.1% versus 82.6%, p = 0.005, two-sided)

4. Muscle discomfort

a. Level 1 (81.4% versus 47.1%, p = 0.001, two-sided)

b. Level 2 (83.0% versus 52.2%, p < 0.000, two-sided)

c. Level 3 (86.3% versus 57.6%, p < 0.000, two-sided)

d. Level 4 (92.3% versus 62.8%, p < 0.000, two-sided)

5. Muscle pain, multi joint pain without swelling or redness

a. Level 1 (84.0% versus 60.0%, p = 0.02, two-sided)

b. Level 2 (84.9% versus 63.8%, p = 0.003, two-sided)

c. Level 3 (85.7% versus 69.6%, p = 0.016, two-sided)

d. Level 4 (90.7% versus 71.7%, p = 0.006, two-sided)

6. Myalgia

a. Level 1 (81.7% versus 58.7%, p = 0.006, two-sided)

b. Level 2 (82.5% versus 62.2%, p = 0.009, two-sided)

c. Level 3 (84.8% versus 65.1%, p = 0.006, two-sided)

d. Level 4 (90.6% versus 67.4%, p = 0.002, two-sided)

7. Prolonged generalised fatigue from levels of exercise that would have been easily tolerated in the patient's premorbid state

a. Level 1 (95.3% versus 80.6%, p = 0.008, two-sided)

b. Level 2 (95.7%, versus 83.7%, p = 0.016, two-sided)

8. Substantial functional impairment

a. Level 1 (86.3% versus 68.6%, p = 0.030, two-sided)

b. Level 2 (86.5% versus 72.3%, p = 0.035, two-sided)

9. Unexplained generalized muscle weakness

a. Level 3 (80.0%, versus 60.3%, p = 0.011, two-sided)

b. Level 4 (86.3% versus 63.2%, p = 0.004, two-sided)

10. Difficulty thinking

a. Level 3 (81.3% versus 65.0%, p = 0.031, two-sided)

11. Forgetfulness

a. Level 4 (78.7% versus 58.8%, p = 0.022, two-sided)

Description of commonly occurring clinical features in the non-CFS/ME comparison group

Similarly for the non-CFS/ME comparison group, the commonly occurring features in at least 25% of cases that were significant at p< 0.05 were identified. This included all features with a possible alternative explanation. The main features however were:

1. Anxiety disorder

a. Level 1 (15.7%- CFS/ME, versus 44.1%- non-CFS/ME, p < 0.000, two-sided)

b. Level 2 (12.7%, versus 43.5%, p < 0.000, two-sided)

c. Level 3 (13.3%, versus 33.8%, p = 0.003, two-sided)

d. Level 4 (9.3%, versus 29.8%, p = 0.004, two-sided)

2. Depressive disorder including endogenous depression

a. Level 1 (27.2%, versus 47.1%, p = 0.029, two-sided)

b. Level 2 (24.8%, versus 47.8%, p = 0.004, two-sided)

c. Level 3 (24.4%, versus 41.5%, p = 0.027, two-sided)

d. Level 4- (17.0%, versus 40.4%, p = 0.003, two-sided)

3. Fibromyalgia

a. Level 4- (12.0%, versus 29.9%, p = 0.017, two-sided)

4. Depression

a. Level 3 (53.8% versus 75.0%, p = 0.009, two-sided)

b. Level 4 (49.1% versus 71.4%, p = 0.007, two-sided)

Table 9 (see Appendix O) shows a summary of the results of univariate analysis performed to identify the single items that were significantly associated with each CFS/ME classification cut-off score. It also gives their p-values from applying the chi-square test of association.

Assessing the impact of unknown data

Although GPs did not complete some questions in the forms sent to them, none of the questionnaires were omitted from the analyses due to missing data. Two different sensitivity analyses were carried out to investigate the effect of ‘don’t know’ or undecided responses.

Firstly, two datasets (datasets 2 and 3) were created in addition to the original dataset (dataset 1) during the univariate analysis, depending on the treatment of the small number of variables, which were undecided in Table 4. This treatment involved imputing the reference values for the independent variables. For dataset 1, the undecided values were not assigned any other value and the dataset remained unadjusted. For dataset 2, ‘do not know responses’ were imputed with a ‘no’ response and the overall number of ‘no’ responses were recalculated to reflect the new inputs. In dataset 3, the ‘do not know responses’ were filled with a ‘yes’ response and the analysis was rerun.

By adopting this approach, it was possible to avoid reducing the sample size and the possibility of bias with the dataset which could have occurred if cases with undecided values had been eliminated from the dataset. The stable sample size also enabled comparison across the different datasets.

Secondly, each dataset was further sub-divided at four levels as described previously according to the CFS/ME classification cut–off score which was based on the average of the reviewers’ scores.

The variables associated with either CFS/ME or non-CFS/ME which remained consistently statistically significant across all the 3 datasets (refer to Table 9) i.e. at all levels during the univariate analysis included:

- a reduction in activity to less than 50% of the patient's premorbid activity
- muscle discomfort
- anxiety disorder
- post-exertional malaise
- muscle pain, multijoint pain without swelling or redness
- myalgia
- swollen lymph nodes

There was consistency of representation of significant variables across the 3 datasets (i.e. variables found to be significant in dataset 1 were also significant for at least one subset of datasets 2 and 3). This indicated that cases with undecided values did not differ in analytically important ways from cases where values were present.

Table 9 Univariate analysis of CFS/ME symptom criteria and co morbid conditions (see Appendix O)

	Dataset 1				Dataset 2				Dataset 3			
Classification cut-off score of each category	A	B	C	D	A	B	C	D	A	B	C	D
50% decrease in activity compared to premorbid	0.000	0.003	0.016	0.005	0.000	0.000	0.000	0.000	0.001	0.019	0.045	0.01
Muscle discomfort	0.000	0.000	0.000	0.000	0.000	0.001	0.000	0.000	0.000	0.000	0.000	0.000
Anxiety disorder	0.000	0.000	0.003	0.004	0.000	0.000	0.005	0.006	0.001	0.000	0.001	0.001
Severe disabling fatigue affecting physical and mental functioning	0.001	0.003	0.005	0.07	0.000	0.001	0.000	0.016	0.001	0.004	0.008	0.084
Post-exertional malaise > 24 hours	0.002	0.008	0.009	0.009	0.01	0.044	0.002	0.009	0.003	0.01	0.021	0.015
Muscle pain, multi-joint pain without swelling or redness	0.005	0.005	0.009	0.002	0.023	0.021	0.005	0.000	0.003	0.004	0.013	0.004
Myalgia	0.006	0.009	0.006	0.002	0.044	0.046	0.006	0.000	0.004	0.006	0.009	0.004
Prolonged generalised fatigue from exercise	0.008	0.016	0.151	0.173	0.07	0.214	0.04	0.044	0.009	0.014	0.2	0.218
Substantial functional impairment	0.016	0.035	0.388	0.105	0.03	0.067	0.226	0.068	0.014	0.031	0.437	0.117
Difficulty thinking	0.017	0.132	0.031	0.055	0.133	0.527	0.037	0.042	0.008	0.076	0.044	0.08
Swollen lymph nodes	0.025	0.015	0.014	0.004	0.043	0.031	0.016	0.003	0.005	0.002	0.072	0.113
Migraine	0.033	0.273	0.525	0.806	0.045	0.354	0.455	0.711	0.015	0.094	0.928	0.778
Hypothyroidism	0.05	0.287	0.107	0.019	0.059	0.302	0.13	0.021	0.031	0.25	0.029	0.016
Painful lymph nodes	0.057	0.024	0.058	0.024	0.113	0.048	0.075	0.015	0.005	0.005	0.067	0.211
Excessive irritability	0.061	0.071	0.215	0.896	0.321	0.555	0.54	0.84	0.009	0.005	0.095	0.968
Unexplained generalized muscle weakness	0.078	0.124	0.011	0.004	0.027	0.047	0.001	0.001	0.165	0.225	0.044	0.009
Hypersensitivity to noise	0.082	0.416	0.221	0.045	0.195	0.693	0.154	0.005	0.037	0.21	0.499	0.55
Infection at onset & laboratory evidence	0.084	0.059	0.056	0.071	0.105	0.058	0.053	0.029	0.12	0.16	0.156	0.481
Mild fever or chills	0.087	0.022	0.027	0.03	0.097	0.036	0.017	0.009	0.136	0.03	0.105	0.169
Migratory arthralgia without joint swelling or redness	0.094	0.046	0.171	0.018	0.136	0.058	0.076	0.004	0.077	0.057	0.532	0.151
Generalised headaches	0.097	0.052	0.006	0.007	0.131	0.113	0.005	0.002	0.095	0.031	0.016	0.041
Substantial impairment in short-term memory	0.105	0.359	0.114	0.013	0.208	0.411	0.041	0.002	0.089	0.38	0.301	0.073
Multiple Chemical Sensitivity	0.106	0.106	0.03	0.314	0.109	0.096	0.042	0.398	0.283	0.531	0.012	0.027
Sore throat	0.123	0.042	0.11	0.216	0.175	0.045	0.087	0.1	0.081	0.082	0.29	0.854
Photophobia	0.157	0.232	0.241	0.468	0.23	0.311	0.281	0.373	0.041	0.101	0.22	0.947
Orthostatic intolerance/other autonomic manifestation	0.18	0.232	0.132	0.019	0.23	0.311	0.125	0.005	0.124	0.114	0.331	0.778
Forgetfulness	0.197	0.173	0.057	0.022	0.674	0.777	0.055	0.012	0.089	0.062	0.096	0.051
Depression	0.26	0.051	0.009	0.007	0.109	0.012	0.021	0.035	0.408	0.115	0.007	0.003
Perceptual or sensory disturbances	0.364	0.486	0.102	0.128	0.661	0.754	0.064	0.061	0.048	0.126	0.447	0.664
Transient visual scotomata	0.387	0.563	0.602	0.394	0.478	0.719	0.657	0.371	0.057	0.037	0.392	0.907
Loss of thermostatic ability	0.438	0.244	0.172	0.047	0.661	0.465	0.143	0.023	0.167	0.057	0.426	0.342
New onset of short term memory impairment	0.449	0.37	0.204	0.116	0.547	0.489	0.104	0.049	0.382	0.287	0.553	0.392
Fibromyalgia Syndrome	0.467	0.456	0.264	0.017	0.413	0.35	0.305	0.028	0.721	0.923	0.24	0.011
Debilitating fatigue not relieved by bed rest	0.523	0.773	0.75	0.282	0.349	0.835	0.104	0.038	0.583	0.705	0.971	0.395
Hyperventilation syndrome	0.602	0.119	0.457	0.207	0.585	0.121	0.512	0.234	0.975	0.207	0.068	0.029
Intolerance of extremes of heat and cold	0.653	0.855	0.317	0.085	0.955	0.722	0.281	0.039	0.354	0.366	0.499	0.349

Key to Table 9

A (Sub-set A)	P-values for variables with a classification cut off score of 5
B (Sub-set B)	P-values for variables with a classification cut off score of 6
C (Sub-set C)	P-values for variables with a classification cut off score of 7
D (Sub-set D)	P-values for variables with a classification cut off score of 8
Areas shaded orange	Variables showing significant differences between the disease and non-disease groups (p-value ≤ 0.05) for dataset 1
Areas shaded purple	Variables showing significant differences between the disease and non-disease groups (p-value ≤ 0.05) for dataset 2
Areas shaded blue	Variables showing significant differences between the disease and non-disease groups (p-value ≤ 0.05) for dataset 3

5.5. *Discrimination based on the unweighted sum of binary variables*

An exploratory technique that entails the use of the unweighted ‘sum of binary variables’ (SBV) was applied to the study dataset. This was used to construct a list of symptoms that identify CFS/ME cases from, the other chronic fatigue cases, thereby distinguishing between CFS/ME cases and the non-CFS/ME comparison group.

SBV is a statistical technique which, according to Langbehn and Woolson (1997) “makes no attempt to differentiate the relative importance of individual predictor variables or allow for possible interactions among the variables” (Langbehn, Woolson 1997). Thus it was considered less useful for identifying the combination of predictor variables that would form the mandatory criteria of the case-definition algorithm. However a successful implementation of this technique often leads to a simple and practical discriminatory rule that is easy to understand.

The main focus of the SBV analysis was on features associated with CFS/ME that could potentially form the basis for determining the required number of supportive criteria from variables that are commonly occurring or strongly associated with CFS/ME but not covered as part of the mandatory criteria.

A list of 14 features from independent variables associated with CFS/ME was generated using the results of the previous univariate analysis (refer to Table 9, section 5.4.1). These variables maximized the group separation in a two independent samples t-test used to assess the statistical differences between the two groups (CFS/ME and non-CFS/ME). One (1) of the 14 variables (cognitive disorders), was an accumulated category made of the variables which contributed at an almost similar level to the separation of the groups during the t-test. This category comprised difficulty thinking and forgetfulness.

The 14 variables or questions that were used in the SBV technique included:

1. Severe disabling fatigue affecting physical and mental functioning
2. A reduction in activity to less than 50% of the patient's premorbid activity
3. Muscle discomfort or myalgia
4. Muscle pain, multi joint pain without swelling or redness
5. Prolonged generalised fatigue from levels of exercise that would have been easily tolerated in the patient's premorbid state
6. Post-exertional malaise lasting more than 24 hours
7. Unexplained generalized muscle weakness
8. Swollen or painful lymph nodes
9. Migraine
10. Generalised headaches (of type, severity, or pattern different from headaches the patient may have had in the premorbid state)
11. Mild fever or chills or sore throat
12. Infection at onset corroborated by laboratory evidence
13. Cognitive disorders (difficulty thinking, substantial impairment in short term memory or concentration, forgetfulness)
14. Substantial functional impairment

Within the list provide, each of the variables were further grouped into one or more broad categories to aid presentation of results later in the study. The groups included:

I. Exertion intolerance (2 variables):
   - Prolonged generalised fatigue from levels of exercise that would have been easily tolerated in the patient's premorbid state
   - Post-exertional malaise lasting more than 24 hours

II. Musculoskeletal symptoms (3 variables):
   - Muscle discomfort or myalgia
   - Muscle pain, multi joint pain without swelling or redness

- o Unexplained generalized muscle weakness

III. Neurocognitive symptoms (3 variables)

- o Migraine
- o Generalised headaches (of type, severity, or pattern different from headaches the patient may have had in the premorbid state)
- o Cognitive dysfunction (difficulty thinking, substantial impairment in short term memory or concentration, forgetfulness)

IV. Immune symptoms (3 variables)

- o Mild fever or chills or sore throat
- o Infection at onset corroborated by laboratory evidence
- o Swollen or painful lymph nodes

V. Reduced functional or mental capacity (3 variables)

- o A reduction in activity to less than 50% of the patient's premorbid activity
- o Substantial functional impairment
- o Severe disabling fatigue affecting physical and mental functioning

To use the list of 14 questions, a simple count of the number of positive or "yes" responses to the presence of a particular variable was made. When the total number of "yes" responses equaled or exceeded a pre-determined cut point, then the CFS/ME was predicted otherwise the prediction of non-CFS/ME was made.

Analyses were performed to determine a suitable cut point based on the number of questions required i.e. cut point nine (9) ≥ nine (9) required questions, cut point eight (8) ≥ eight (8) required questions, cut point seven (7) ≥ seven (7) required questions and cut point six (6) ≥ six (6) required questions.

To achieve a reasonable balance between sensitivity and specificity as an increase in one measure, led to the decreasing of the other (Ranawana, Palade 2005), the number of questions reported for the decision rule within each model was between the ranges of six to ten. Outside of this range, very low values of sensitivity or specificity (<50%) were observed which dampened the performance of the model. Hence only the optimal performance measures as demonstrated by the overall accuracy were reported.

The selection of the final decision rule for each model was based on two criteria: (i) the set of ‘yes’ responses (or cut point) which demonstrated the highest sensitivity and (ii) the best overall accuracy.

The utility of the list of questions within each dataset, in arriving at the decision rule for the four models A, B, C and D are presented below.

5.5.1. Model A

Model A was constructed using dataset A. The results of the model indicated a direct relationship between the number of positive responses to any of the questions and the overall accuracy as seen in Table 10 and depicted in Figure 3.

Table 10 Performance measures for Model A

Minimum number of positive responses required for CFS/ME classification (n=14)	Number of CFS/ME incorrectly classified (n=119)	Number of non-CFS/ME incorrectly classified (n= 34)	Sensitivity	Specificity	Overall accuracy
nine (9)	43 (36.7%)	10 (27.8%)	62.7	72.2	64.9
eight (8)	31 (26.5%)	11 (30.6%)	73.7	69.4	72.7
seven (7)	20 (17.1%)	13 (36.1%)	83.1	63.9	78.6
six (6)	12 (10.3%)	18 (50%)	89.8	50.0	80.5

The best performance in terms of the highest sensitivity and overall accuracy was observed when at least six (6) questions had positive responses. Thus a case would be classified as CFS/ME if it had 6 or more ‘yes’ responses to the questions otherwise it would be classified as non-CFS/ME under the model’s decision rule as outlined in the previous section.

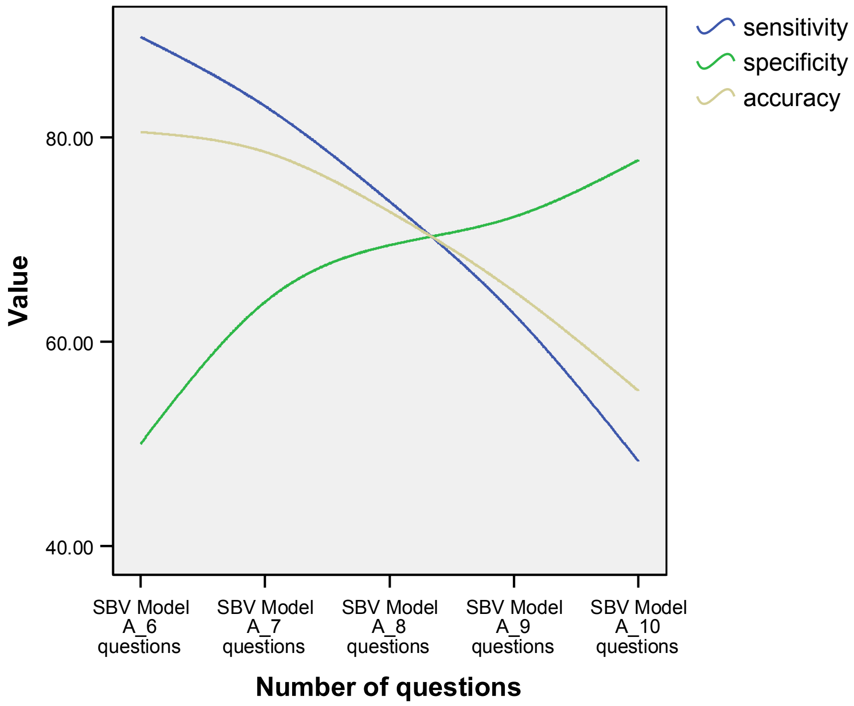


Figure 3 Graph of sensitivity, specificity and accuracy by least number of questions for Model A

The graph plot in Figure 3 shows that an increase in the number of questions selected for case classification for Model A resulted in a corresponding increase in specificity but a decrease in sensitivity and the overall accuracy.

Figure 4 shows box plots in which the boundary of boxes closest to zero indicates 25th percentile, line within boxes marks median, and boundary of boxes farthest from zero indicates 75th percentile. The separation in the total “yes” for the two groups (CFS/ME, non-CFS/ME) for Model A is shown with reference line drawn at 6.

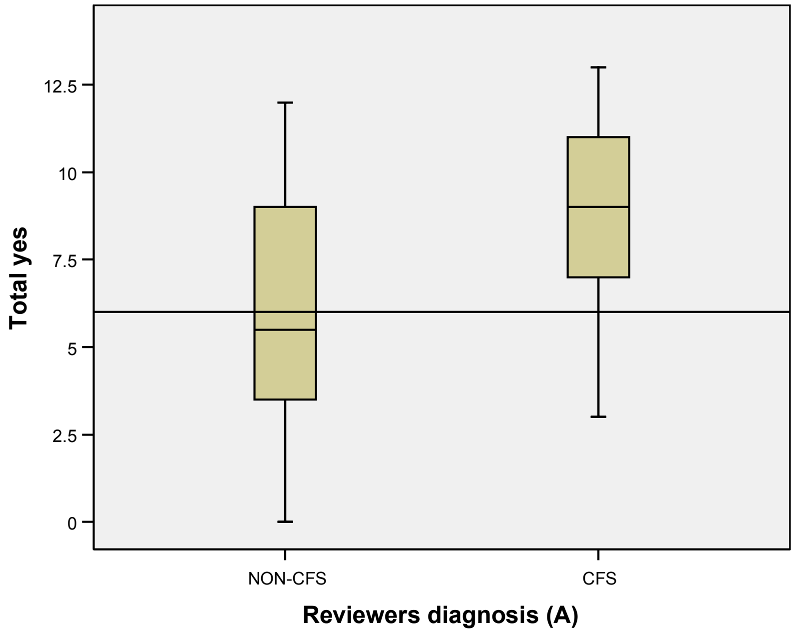


Figure 4 Box plot of the total "yes" answers to 14 questions for the two groups (CFS/ME, non-CFS/ME) in Model A

Application of the two-independent samples t-test (see Table 11), showed that there was a statistically significant difference in the mean "yes" responses between the two groups (t = 4.89, df = 45, p < 0.001 two-sided).

Table 11 Independent Samples Test (Model A)

		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Lower	Upper
Total yes	Equal variances not assumed	10.241	.002	-4.894	45.199	.000	-3.030	.619	-4.277	-1.783

5.5.2. Model B

The performance of the model constructed using dataset B, was found to be moderate as shown in the results of the SBV analysis given as follows:

Table 12 Performance measures for Model B

Minimum number of positive responses required for CFS/ME classification n=14	Number of CFS/ME incorrectly classified (n=106)	Number of non-CFS/ME incorrectly classified (n= 47)	Sensitivity	Specificity	Overall accuracy
nine (9)	37 (35.2%)	16 (33.3%)	66.7	65.4	64.8
eight (8)	26 (24.8%)	19 (39.6%)	73.7	69.4	70.6
seven (7)	16 (15.2%)	22 (45.8%)	84.8	54.2	75.2
six (6)	11 (10.5%)	29 (60.4%)	89.5	39.6	73.9

The performance values shown in Table 12 suggest that optimal model performance with respect to overall accuracy was observed when there were seven (7) positive responses to the questions. Although sensitivity (89.5%) was highest for six (6) positive responses to the 14 questions, at less than 50%, the specificity was very poor compared to the other questions (39.6%) thus impacting on the final overall accuracy (73.9%).

Thus a case would be classified as CFS/ME if it had 7 ‘yes’ responses to the questions otherwise it would be classified as non-CFS/ME under the guide for the decision rule set out at the beginning of this section.

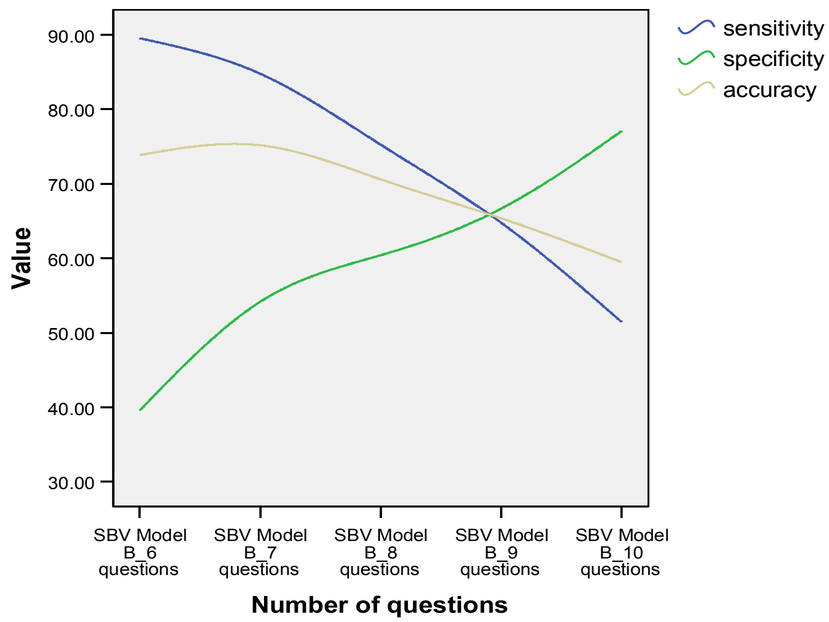


Figure 5 Graph of sensitivity, specificity and accuracy and the number of positive responses for case classification

Figure 5 shows the relationships between the performance measures reflecting that an increase in the number of questions selected for case classification for Model B corresponded with an increase in specificity but a decrease in sensitivity and the overall accuracy.

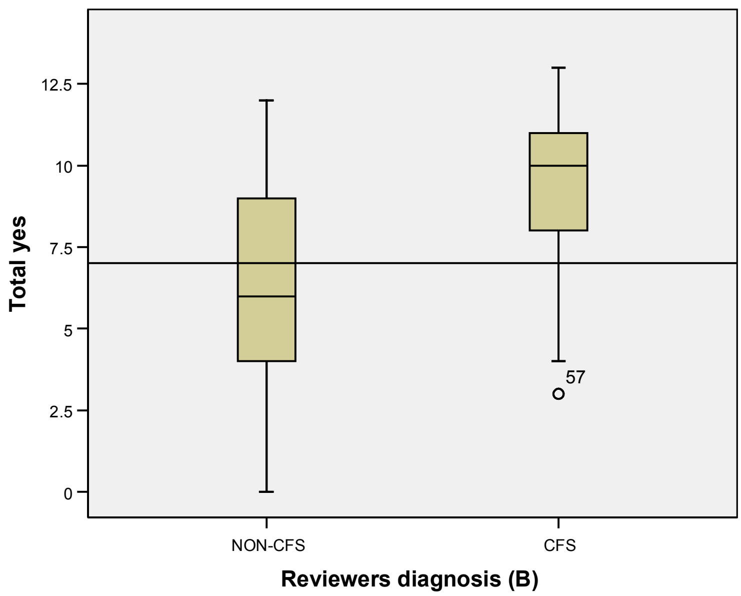


Figure 6 Box plot of the total "yes" responses to 14 questions for the two groups (CFS/ME, non-CFS/ME) Model B

Figure 6 shows box plots in which the boundary of boxes closest to zero indicates 25th percentile, the line within boxes marks the median, and boundary of boxes farthest from zero indicates the 75th percentile. The separation in the total "yes" for the two groups (CFS/ME, non-CFS/ME) for Model B, is shown with reference line drawn at 7 on the y-axis.

Again, application of the two-independent samples t-test showed that there was a statistically significant difference in the mean "yes" responses between the two groups (t = 4.83, df = 69.9, p < 0.001 two-sided) as shown in Table 13.

Table 13 Independent Samples Test (Model B)

		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Lower	Upper
Total yes	Equal variances not assumed	10.486	.001	-4.825	69.992	0.000	-2.565	0.532	-3.625	-1.505

5.5.3. Model C

Model C was constructed using dataset C and the results of the SBV analysis is shown in Table 14.

Table 14 Performance measures for Model C

Minimum number of positive responses required for CFS/ME classification n=14	Number of CFS/ME incorrectly classified (n=84)	Number of non-CFS/ME incorrectly classified (n= 69)	Sensitivity	Specificity	Overall accuracy
nine (9)	19 (22.9%)	20 (28.6%)	77.1	71.4	74.5
eight (8)	13 (15.7%)	28 (40%)	84.3	60.0	73.2
seven (7)	11 (13.3%)	39 (55.7%)	86.7	44.3	67.3
six (6)	7 (8.4%)	47 (67.1%)	91.6	32.9	64.7

Although the highest sensitivity was observed when there were at least six (6) positive responses to the 14 questions, this was not well balanced against specificity (32.9%) which was the lowest value thus impacting on the final overall accuracy (64.7%).

The best performance in terms of the overall accuracy and sensitivity for a number of responses that did not have any values less than 50%, was observed when there were nine (9) questions i.e. a case would be classified as CFS/ME when there were at least nine positive responses to the 14 questions otherwise it would be classified as non-CFS/ME.

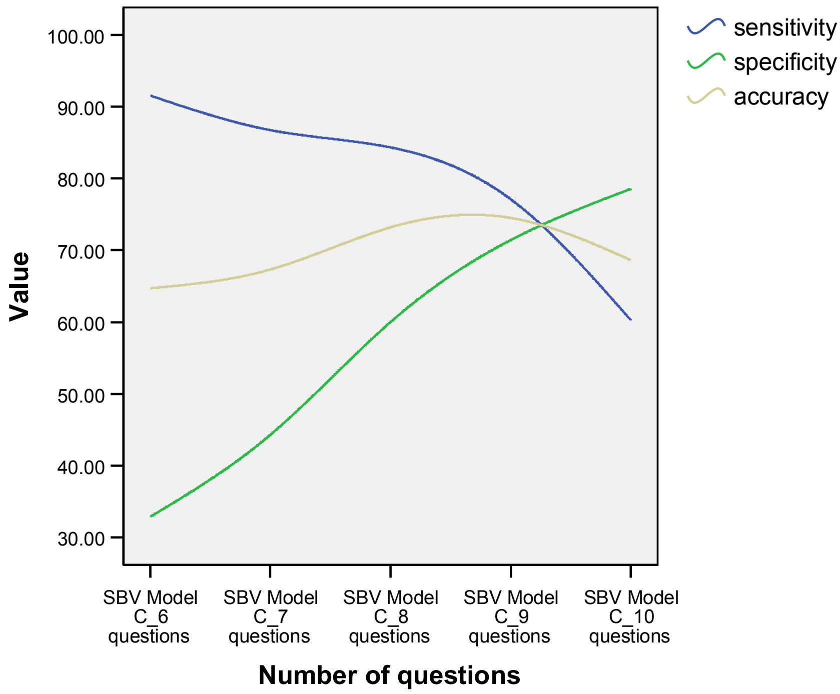


Figure 7 Graph of sensitivity, specificity and accuracy and the number of positive responses to the 14 questions

The graph shows the relationships between the performance measures at different cut points (number of questions). Under the decision rule, a case would be classified as CFS/ME if there are nine positive responses, otherwise class as non-CFS/ME.

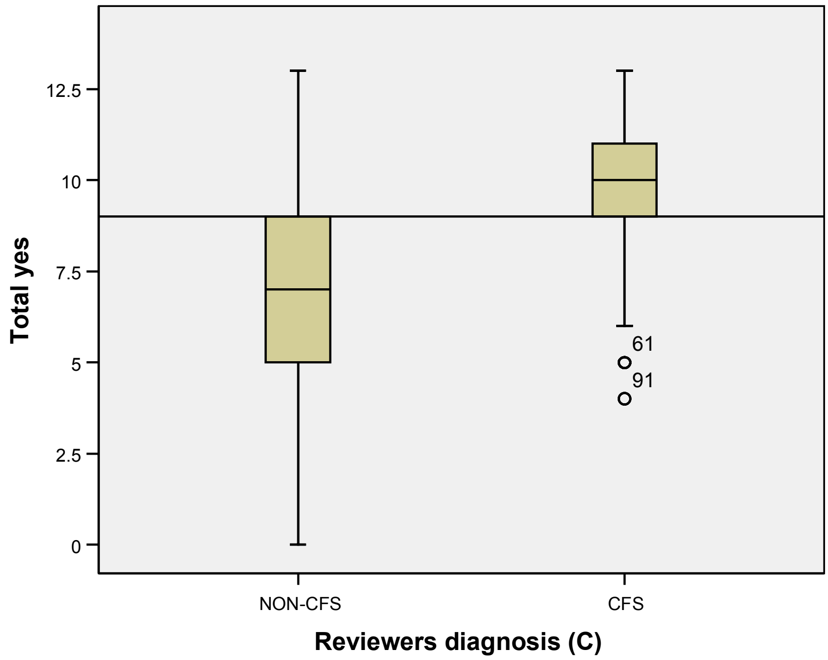


Figure 8 Box plot of the total "yes" for the two groups (CFS/ME, non-CFS/ME) Model C

Figure 8 shows box plots in which boundary of boxes closest to zero indicates 25th percentile, line within boxes marks median, and boundary of boxes farthest from zero indicates 75th percentile. The separation in the total "yes" for the two groups (CFS/ME, non-CFS/ME) for Model C is also shown with the reference line drawn at 9.

The application of the two-independent samples t-test (Table 15) also showed that there was a statistically significant difference in the mean "yes" responses between the two groups (t = 6.16, df = 121, p < 0.001 two-sided).

Table 15 Independent Samples Test (Model C)

		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference Lower	Upper
Total yes	Equal variances not assumed	9.432	.003	-6.158	120.955	0.000	-2.704	0.439	-3.573	-1.835

5.5.4. Model D

The results of the SBV analysis for Model D was using dataset D are shown in Table 16.

Table 16 Performance measures for Model D

Minimum number of positive responses required for CFS/ME classification (n=14)	Number of CFS/ME incorrectly classified (%) n=54	Number of non-CFS/ME incorrectly classified (%) n= 99	Sensitivity	Specificity	Overall accuracy
ten (10)	16 (29.6%)	27 (27.3%)	70.4	72.7	71.9
nine (9)	8 (14.8%)	38 (38.4%)	85.2	61.6	69.9
eight (8)	4 (7.4%)	48 (48.4%)	92.6	51.5	66.0
seven (7)	3 (5.6%)	60 (60.6%)	94.4	39.4	58.8
six (6)	2 (3.7%)	71 (71.4%)	96.3	28.3	52.3

Although the highest sensitivity was observed when there were at least six (6) positive responses to the 14 questions, this was not well balanced against specificity (28.9%) which was the lowest value thus impacting on the final overall accuracy (52.3%). The highest overall accuracy was observed when there was a minimum of ten (10) positive responses i.e. a case would be classified as CFS/ME when there were at least 10 positive responses to the 14 questions otherwise it would be classified as non-CFS/ME.

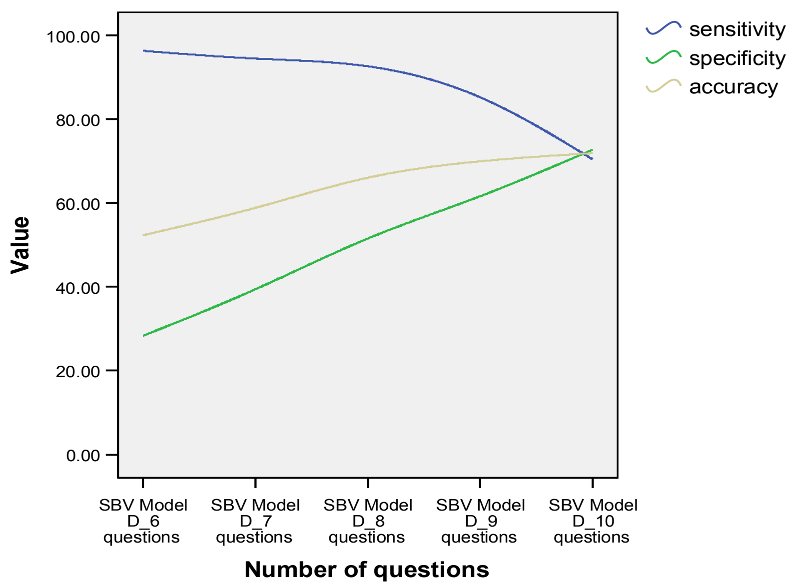


Figure 9 Graph of sensitivity, specificity and accuracy by least number of questions

The graph in figure 9 shows that near the highest point of accuracy, there is an intersection with the sensitivity and specificity. This demonstrates the closeness in balance between the two measures when there are ten positive responses to the 14 questions. Therefore, under this decision rule, a case would be classified as CFS/ME if there are ten positive responses, otherwise class as non-CFS/ME.

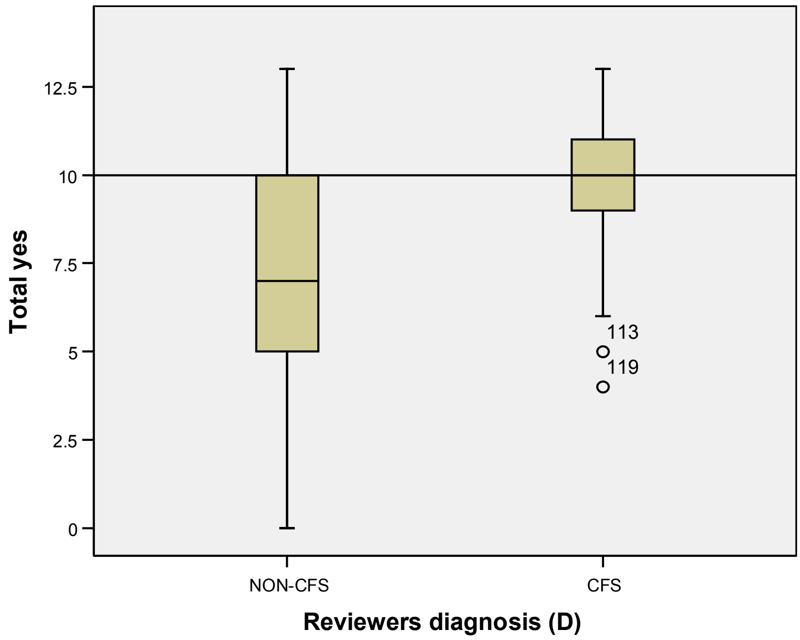


Figure 10 Box plot showing the total number of positive responses to the 14 questions for the two groups (CFS/ME, non-CFS/ME) Model D

Figure 10 shows box plots in which the boundary of boxes closest to zero indicates the 25th percentile, the line within the boxes marks the median, and the boundary of boxes farthest from zero indicates 75th percentile. The separation in the total "yes" for the two groups (CFS/ME, non-CFS/ME) for Model D is also seen with a reference line drawn at 10.

The application of the two-independent samples t-test in Table 17, showed that there was a statistically significant difference in the mean "yes" responses between the two groups (t = 6.83, df = 149, p < 0.001 two-sided).

Table 17 Independent Samples Test (Model D)

		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Lower	Upper
Total yes	Equal variances not assumed	20.693	.000	-6.826	148.832	0.000	-2.685	0.393	-3.463	-1.908

5.5.5. Summary of performance measures using the SBV method

Using the SBV, it was possible to identify a set of questions that could discriminate reasonably well between CFS/ME cases and the non-CFS/ME comparison group. The list of variables however focused on features that had a significant relationship with the CFS/ME group (refer to section 5.4.1), and the number of positive responses required to classify a case. This made it possible to assess the effect of the cut point on the performance of the model.

Further, the order of performance for each model is similar to that obtained in the discriminant analysis (discussed in the next section) as summarised in Table 18.

Table 18 Summary of the best performance measures from the SBV analysis

Model	Minimum number of positive responses required for CFS/ME classification n=14	Proportion of CFS/ME incorrectly classified (%)	Proportion of non-CFS/ME incorrectly classified (%)	Sensitivity	Specificity	Overall accuracy
A	six (6)	10.3	50	89.8	50.0	80.5
B	seven (7)	15.2	45.8	84.8	54.2	75.2
C	nine (9)	22.9	28.6	77.1	71.4	74.5
D	ten (10)	29.6	27.3	70.4	72.7	71.9

The steps taken to establish the best predictor variables for CFS/ME from the list are described in the next section on discriminant analysis.

5.6. Discriminant analysis

A two-group discriminant analysis was performed based on the binary prediction model i.e. the presence or absence of CFS/ME. In general, multivariate discriminant analysis is typically considered to be robust to violations and the use of dichotomous variables in discriminant analysis does not greatly affect conclusions (Lachenbruch 1975).

A primary objective of the study was to determine criteria which distinguished between CFS/ME cases and other chronic fatiguing illnesses of unexplainable cause. Thus discriminant analysis was performed on the study sample excluding ten (10) cases with clear possible alternative medical or psychiatric illnesses, as defined by the clinical research definitions (n=18). This initial analysis was conducted using dataset 2 to determine the best combination of variables that define CFS/ME (Hand 1983). The analysis was then rerun again on the total study sample (N=162) now including the cases that were previously excluded (i.e. with the possible alternate explanations) to assess if there were any differences in the predictors and the performance of the final models.

Dataset 2 which included undecided values that were coded as negative (0) was used in preference to dataset 3 which included undecided values coded as positive (1), because research shows that the absence of clinical signs and symptoms is often not documented or reported, and even not discussed during medical consultations on the assumption by the doctor that issues which were not revealed by the current complaint were negative (Gerbert, Hargreaves 1986).

All four subsets of dataset 2 using the different classification threshold levels were included in the analysis to identify possible patterns across case identification criteria.

The discriminant analysis involved firstly, the specification of the groups to be predicted i.e. CFS/ME and non-CFS/ME and then the selection of variables showing a statistically significant association with CFS/ME in univariate tests shown in Table 9.

There were a total of 11, 14, 17 and 28 significant variables for datasets A, B, C and D respectively.

Secondly, these significant variables were entered in SPSS in a stepwise fashion using Wilks' lambda criterion and combined into models with weighted coefficients so that differences between the groups were maximized. The sign of the coefficients indicated the probability of being associated with a particular group and the size or weight of a coefficient indicated the strength of that coefficient in discriminating between the groups (Evans 1978). Both CFS/ME and non-CFS/ME comparison groups were unequal in size, thus to ensure that accurate results were obtained, the baseline estimates of probability were calculated according to the group size (by selecting the ‘compute according to group size’ option in the classify option’).

Thirdly, a classification summary table was produced to determine if it was possible to differentiate between groups. To ensure the reliability of the results of the summary table, a leave-out-one cross-validation analysis was also included at this stage. In checking the robustness of the discriminant functions of the discriminant analysis, the functions were computed consecutively leaving out one sample. The group membership of the removed observation was then predicted by the classification functions derived from the rest of the sample other than that case. This controlled for the classification bias inherent in generating discriminant function with the same set of cases it is subsequently used to classify (Johnson, R. A. and Wichern, D. W. 1998).

A classification matrix was constructed and analysed as a 2 x 2 contingency table. The matrix showed the frequency of correct and incorrect classification resulting from the decision rule. This enabled further assessment of the accuracy of the discriminant analysis at each threshold. Kappa (κ) coefficient and traditional sensitivity analysis (sensitivity and specificity) were used to evaluate how well the models correctly classified CFS/ME status compared with the reviewers.

The results are presented in subsequent sections.

5.6.1. Results of discriminant analyses

I. Summary of Canonical Discriminant Functions for the model derived from dataset with a classification threshold of 5 (Model A)

Table 19 displays both discriminant and classification function coefficients which enable examination of the relative standing of measurements and the contribution of individual variables to the overall discrimination.

The significant variables for the model with the classification cut-off score of 5 were: a reduction in activity to less than 50% of the patient's premorbid activity (@50no), severe disabling fatigue affecting physical and mental functioning (sev_fatno), muscle discomfort (musdisno) and anxiety disorder (anxtyno). This combination distinguished best between the CFS/ME and non-CFS/ME groups for the model derived from subset A.

Table 19 Discriminant and Classification Function Coefficients Model A

	Discriminant functions		Classification functions	
Independent variabl	Unstandardised	Standardised	CFS/ME	non-CFS/ME
sev_fatno	1.403	0.442	8.532	6.088
@50no	1.624	0.612	5.527	2.698
musdisno	0.986	0.437	3.138	1.420
anxtyno	-1.727	-0.683	-1.837	1.171
(Constant)	-2.826		-7.779	-4.771

The formula for the discriminant or Z score (unstandardised) for model A was

-2.826 + 1.624(@50no) + 1.403 (sev_fatno) + 0.986 (musdisno) -1.727 (anxtyno)

The coefficients of the classification function were not included in the Z score as their purpose was to assign or classify cases to CFS/ME or non-CFS/ME comparison groups and they were not necessary for the decision rule. However, the classification function for CFS/ME cases was 8.532sev_fatno + 5.527@50no + 3.138musdisno - 1.837anxtyno – 7.779. Further, on subtracting the classification coefficients for the non-CFS/ME group

from the coefficients for the CFS/ME group, Fisher's classification function for the above analysis was thus found to classify a patient as belonging to the CFS/ME group if

-3.008 + 2.444 x sev_fatno + 2.829 x @50no + 1.718xmusdisno -3.008 x anxtyno > 0

and to classify as belonging to the non-CFS/ME group otherwise i.e. if

-3.008 + 2.444 x sev_fatno + 2.829 x @50no + 1.718xmusdisno -3.008 x anxtyno < 0

In the above equations the variable sev_fatno takes the value of "1" if severe fatigue is presented and takes the value "0" otherwise. Likewise the variables "@50no", "musdisno" and "anxtyno" take the value "1" if presented and take the value "0" otherwise.

The separation of the two groups as described by box plots of the distribution of the discriminant scores is seen in Figure 11.

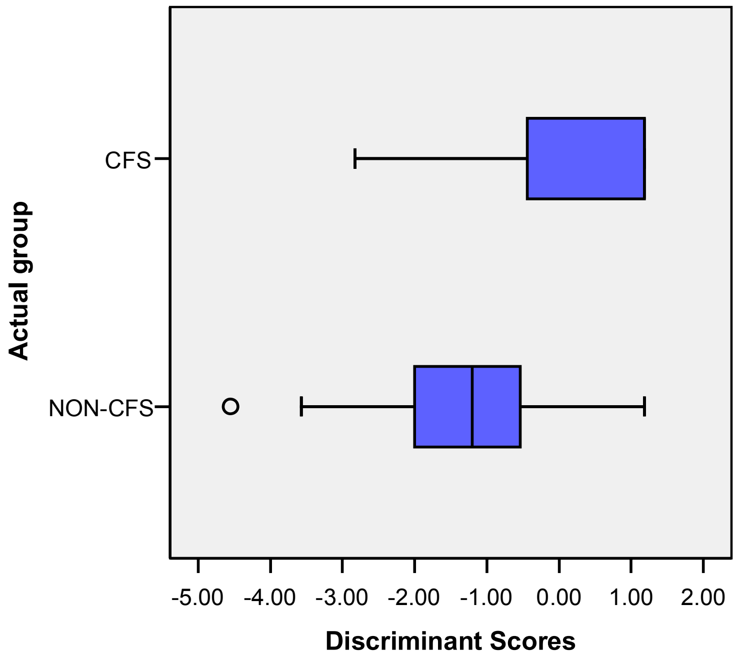


Figure 11 Box plots of discriminant scores for CFS/ME versus non-CFS/ME in the actual group

The box plots in Figure 11 above represent the distributions of discriminant scores generated using the CFS/ME versus non-CFS/ME for the actual group. The shaded box of each plot represents the interquartile range of the distribution. The dividing line represents the median, and the whiskers or brackets to the right and left of each box represent the maximum and minimum values, respectively. There is an outlier in the non-CFS group indicating that the observation did not match the profile of the non-CFS/ME group. An overlap of the whiskers of the scores for CFS/ME versus the non-CFS/ME comparison group is also noted.

Overall significance

The discriminant analysis produced only one discriminant function. Table 20 presents Eigenvalues, the percentage of variance, the cumulative percentage, and canonical correlations for this function.

Table 20 Model fit: Canonical Discriminant Functions Model A

Function	Eigenvalue	Percentage of Variance		Canonical Correlation	Wilks' Lambda	Chi-square	df	Sig.
		Function %	Cumulative %					
1	.566(a)	100.0	100.0	0.601	0.639	62.794	4	.000

The Eigenvalue (ratio of the between-groups sum of squares to the within-groups sum of squares) of the discriminant function was 0.566. The canonical correlation (a measure of the association between the discriminant scores and the groups) was 0.601 indicating a high, but not perfect, association between group membership and derived discriminant score.

Overall significance of the model

The overall test of significance using Wilks' lambda Λ was computed as the ratio of between the between groups variance to the within groups variance. Wilk's

lambda ranges from 0 to 1 and increasingly smaller values of lambda indicate increasing better group separation."

This proportion of the total variance in the discriminant scores not explained by differences among the groups was 0.639 for Model A.

The significance of lambda tested with the χ^2 test was statistically significant ($p < 0.001$). This indicated that the model should be retained as the group means (centroids) were unequal and different with discriminatory powers.

The significance of individual variables in dataset A derived by running discriminant analysis on each variable independent of other variables are presented in (Appendix Q).

Structure matrix

The structure matrix is an indication of within-group correlations of each predictor variable and the discriminant function. The correlations (demonstrated by the standardised discriminant function coefficients) represent the weighting each variable has on the function.

Table 21 displays the correlations between individual variables and functions in the structure matrix. These are listed in the order of the importance of each individual variable within the function and its importance for predicting CFS/ME cases compared to the non-CFS/ME comparison group.

Table 21 Structure Matrix of correlations between predictor variables and discriminant functions Model A

Independent variables	Function 1
@50no	0.558
sev_fatno	0.456
anxtyno	-0.409
musdisno	0.406

Pooled within-groups correlations between discriminating variables and standardized canonical discriminant functions
Variables ordered by absolute size of correlation within function.

According to Table 21, the most important predictor variables for determining membership of the CFS/ME group (variables with positive values) from the non-CFS/ME group (variables with negative values) were a reduction in activity to less than 50% of the patient's premorbid activity, followed by severe disabling fatigue affecting physical and mental functioning, muscle discomfort; anxiety disorder was a good negative predictor of the function.

Group centroids

The average predicted solution of the discriminant function represented by group centroids (also known as within-group means) are displayed in Table 22.

Table 22 Group Means (Centroids) of Discriminant Functions Model A

CFS/ME is 5 or>	Function 1
CFS/ME	0.423
non-CFS/ME	-1.318

Unstandardised canonical discriminant functions evaluated at group means

The average discriminant scores for CFS/ME and non-CFS/ME were 0.423 and -1.318 respectively. A positive score indicates that a patient is likely to have CFS/ME, while a negative score (less than zero) indicates that a patient is not likely to have CFS/ME.

Classification matrix of the discriminant analysis

Table 23 displays the degree of success of the classification for the model, the number and percentage of cases correctly classified and misclassified. It is a cross tabulation of actual group membership and predicted group membership, plus a classification of the ungrouped cases.

Table 23 Classification Results (b,c) Model A

Predicted Group Membership	Actual Group									
	Original						Cross-validated(a)			
	N			%			*N*		%	
	CFS/ ME	non-CFS/ME	Ungrouped cases	CFS/ ME	non-CFS/ME	Ungrouped cases	CFS/ ME	non-CFS/ME	CFS/ ME	non-CFS/ME
CFS/ME	104	14	3	94.5	42.9	37.5	103	18	94.5	51.4
non-CFS/ME	6	20	5	5.5	57.1	62.5	6	17	5.5	48.6
Total	110	34	8	100.0	100.0	100.0	109	35	100.0	100.0

a Leave-one-out classification was performed as a form of cross-validation of the classification table. Cross validation was done only for those cases in the analysis i.e. each case was classified by the functions derived from all cases other than that case and thought to give a better estimate of what classification results would be in the population. The option for the cross validation was selected in the discriminant section of SPSS using the following steps: analyze, classify, discriminant; select variables; click Classify; select Leave-one-out classification; continue).
b 85.4% of original grouped cases correctly classified.
c 83.3% of cross-validated grouped cases correctly classified.

5.6.2. Performance of Model A

Sensitivity analyses (sensitivity and specificity) are tools for evaluating how well a test identifies cases relative to an established gold standard (Rothman, Greenland 1998). The sensitivity, specificity, positive predictive value and positive likelihood ratio of the case-defining characteristics in CFS/ME cases for Model A were determined using the reviewers’ judgment as the gold standard.

The degree to which the CFS/ME cases in the predicted group membership represented CFS/ME cases in the actual group membership as identified by the reviewers (i.e. the accuracy or validity) was assessed in terms of sensitivity and specificity. The sensitivity of Model A for a CFS/ME case is represented by the proportion of CFS/ME cases in the predicted group membership who presented as positive cases according to the reviewers. Specificity was represented by the proportion of all non-CFS/ME group members in the predicted group membership who did not present as cases (i.e. the non-CFS/ME comparison group) according to the reviewers.

The likelihood ratio is the probability of a specified combination of signs and symptoms in those with CFS/ME divided by the probability of the combination in those without CFS/ME, that is, the sensitivity divided by the false-positive rate. It enables the

estimation of the increase or decrease of the probability that a case will be classified as CFS/ME when a specified combination of signs and symptoms is present or absent.

A likelihood ratio that is equal to one would indicate equal pre and post-test probabilities. A likelihood ratio that is greater than one would increase the probability that CFS/ME is present, and the higher the likelihood ratio, the greater this increase. Conversely when less than one, it would decrease the probability of CFS/ME and the smaller the likelihood ratio, the greater the decrease in probability (Jeaschke, Guyatt & Sackett 1994a, Jeaschke, Guyatt & Sackett 1994b).

Performance of the case-definition algorithm

The cases highlighted on the diagonal in Table 23 are those that were correctly classified. According to the table, 103 CFS/ME cases (94.5%) were correctly classified; 6 CFS/ME cases (5.5%) were incorrectly classified to the non-CFS/ME comparison group. The results demonstrate that Model A is fairly robust as the percentages of the actual and predicted groups were similar. The overall accuracy was 85.4% and the prediction accuracy (percentage of cross-validated cases correctly classified) was 83.3%. Thus the classification was incorrect for only 2.1% of cases.

The performance of the model is depicted in the graph in Figure 12 using a receiver operating characteristic curve. This shows a graphical plot of the sensitivity vs. (1 - specificity) as discrimination threshold is varied. At a high threshold, there will be almost no false positives or many true positives as both would be close to zero (point low down and to the left of the ROC curve) (Van Schalkwyk 2003). As the test threshold moves towards a lower value, the number of true positives increases (rather dramatically at first, so the ROC curve moves steeply up) and then reaches a region where there is an increase in false positives and slopes off as the test threshold moves down to a lower values.

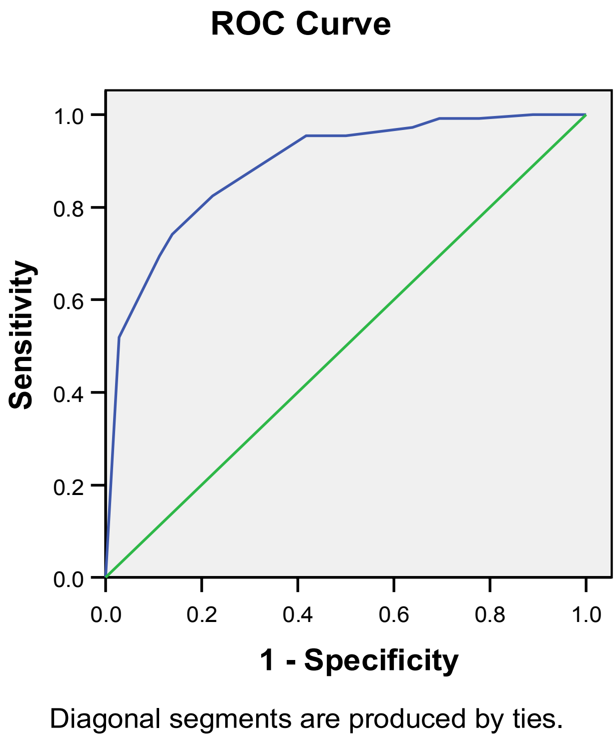


Figure 12 ROC Curve depicting how well the classification results reflect the actual group. The area under the curve which is an indication of the discriminant ability was 0.888

Figure 12 shows that the results are fairly accurate and that the model predicts better than guessing. The diagonal line reflects the characteristics of a test with no discriminating power. The closer the graph gets to the upper left hand corner (0.0, 1.0), the better the test is at discriminating between cases and non-cases.

An index of the goodness of the test is the area under the curve (AUC). A perfect test would have an area of 1.0, whilst a non-discriminating test (one which falls on the diagonal) would have an area of 0.5. Thus the further blue curve lays above the green reference line, the more accurate the test (O'Connell, Myers 2002). According to Hosmer and Lemeshow (2000), the AUC-value provides a single measure of overall accuracy that is not dependent upon a particular threshold (Hosmer, Lemeshow 2000). Values above 0.7 describe an acceptable discrimination, values between 0.8 and 0.9 denote good discrimination and for a value above 0.9, discrimination is excellent (Hosmer, Lemeshow 2000).

The performance of the model was also assessed with and without exclusionary conditions i.e. by excluding cases. Presenting the results in this way prevents limitations on the interpretation of the results which can then be extended to different patients including those with possible alternative illnesses where the diagnosis still remains unclear. It also enables the assessment of the impact of these conditions on the performance of the test. The results are summarised in Table 24.

Table 24 Summary of the performance of Model A

Performance measures	Values (95% confidence intervals in brackets)	
	Cases with possible alternative diagnoses excluded	*Cases with possible alternative diagnoses included*
Sensitivity (true positive rate)	0.945 (95% CI 0.902-0.975)	0.950 (95% CI 0.910-0.977)
Specificity (true negative rate)	0.571 (95% CI 0.438-0.665)	0.629 (95% CI 0.494-0.721)
Positive predictive value (PPV)	0.873 (95% CI 0.833-0.901)	0.897 (95% CI 0.859-0.923)
Negative predictive value (NPV)	0.769 (95% CI 0.589-0.895)	0.786 (95% CI 0.618-0.901)
False negative rate	0.055	0.050
False positive rate	0.428	0.371
Positive likelihood ratio (PLR)	2.204	2.556
Negative likelihood ratio (NLR)	0.096	0.080
Overall accuracy	0.854	0.876
Kappa (p=0.000)	0.566	0.622

The results show that the impact of excluding cases with possible alternative diagnoses was limited as values remained within the 95% confidence interval range. The sensitivity and specificity values were however increased when cases were not excluded from the analysis. The kappa value of 0.566 indicated moderate agreement between the actual and predicted group membership.

Validity of individual questions

When assessed independently of each other, the overall accuracy of CFS/ME predictors in Model A in order of individual importance was:

- 79.9% for a reduction in activity to less than 50% of the patient's premorbid activity
- 79.2% for severe disabling fatigue affecting physical and mental functioning

- 77.3% for muscle discomfort, swollen lymph nodes, myalgia, post-exertional malaise lasting more than 24 hours and unexplained generalised muscle weakness.

To explore further the specific results of the CFS/ME and non-CFS/ME group, the sensitivity, specificity, positive predictive values (PPV) and PLR (positive likelihood ratio) of each clinical feature within the CFS/ME group were examined, using the reviewers' judgement as the gold standard (Table 25). As sensitivity increased toward 100%, the proportion of cases that were classified as not having CFS/ME but who had the condition, (false negatives) decreased toward 0. With the exception of severe disabling fatigue affecting physical and mental functioning, and a reduction in activity to less than 50% of the patient's premorbid activity, all other criteria independent of each other were uninformative (positive likelihood ratio =1) with respect to the discrimination of cases.

Table 25 Sensitivity, specificity, positive predictive value (PPV) and positive likelihood ratio (PLR) of CFS/ME features in cases in Model A using the reviewers' judgement as the gold standard (confidence intervals reported in brackets).

Clinical features	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**PLR**
50% decrease in activity compare to premorbid activity	88.07 (80-93)	48.57 (31-66)	84.21 (76-90)	1.71 (1.23-2.38)
Severe disabling fatigue affecting physical and mental functioning	93.57 (87-97)	31.42 (16-49)	80.95 (73-87)	1.36 (1.08-1.71)
Muscle discomfort	100 (96-100)	0 (0-10)	75.69 (67-82)	1 (1-1)
Swollen lymph nodes	100 (96-100)	0 (0-10)	75.69 (67-82)	1 (1-1)
Myalgia	100 (96-100)	0 (0-10)	75.69 (67-82)	1 (1-1)
Post-exertional malaise	100 (96-100)	0 (0-10)	75.69 (67-82)	1 (1-1)
Muscle pain, multijoint pain without swelling or redness	100 (96-100)	0 (0-10)	75.69 (67-82)	1 (1-1)
Unexplained generalised muscle weakness	100 (96-100)	0 (0-10)	75.69 (67-82)	1 (1-1)

Summary of the discriminant analysis for Model A

The discriminant analysis for Model A thus produced a decision rule which showed that a combination of a reduction in activity to less than 50% of the patient's premorbid activity, severe disabling fatigue affecting physical and mental functioning and muscle discomfort and anxiety disorder distinguished CFS/ME cases from the non-CFS/ME comparison group. Anxiety disorder (absent in the CFS/ME group) had the least discriminatory power and was only useful for ascertaining the non-CFS/ME comparison group. Other variables such as swollen lymph nodes, myalgia, post-exertional malaise and generalised muscle weakness though common in CFS/ME cases, were not able to provide any additional discriminatory power between CFS/ME cases and the non-CFS/ME comparison group and thus had no impact on the statistical model.

The discriminant classifier identified an exclusionary criterion as a significant predictor of the non-CFS/ME group when all cases were included in the analysis. Apart from this, there were no differences in the predictors of CFS/ME and non-CFS/ME group membership when discriminant analysis was conducted on the dataset with and without cases having a possible alternative explanation for illness.

II. Summary of Canonical Discriminant Functions for the model derived from the dataset with a classification threshold of 6 (Model B)

Table 26 displays the discriminant and classification function coefficients which enable examination of the relative standing of measurements and the contribution of individual variables to the overall discrimination.

The significant variables for the model with the classification cut-off score of 6 were: a reduction in activity to less than 50% of the patient's premorbid activity (@50no), severe disabling fatigue affecting physical and mental functioning (sev_fatno), muscle discomfort (musdisno), anxiety disorder (anxtyno), depression (depressno). This combination distinguished best between the CFS/ME and non-CFS/ME groups for the model derived from subset B.

Table 26 Discriminant and Classification Function Coefficients Model B

	Discriminant functions		Classification functions	
Independent variables	Unstandardised	Standardised	CFS/ME	non-CFS/ME
sev_fatno	0.983	0.315	8.164	6.389
@50no	1.600	0.607	5.364	2.475
musdisno	0.873	0.389	2.696	1.121
anxtyno	-1.814	-0.701	-2.708	0.566
depressno	-0.752	-0.363	0.917	2.275
(Constant)	-2.119		-7.980	-5.445

The discriminant Z score was = -2.119 + 0.983 (sev_fatno) + 1.600 (@50no) + 0.873 (musdisno) -1.814 (anxtyno) – 0.752 (depressno)

The estimate of the classification function for CFS/ME cases was 8.164sev_fatno + 5.364@50no + 2.696musdisno – 2.708anxtyno + 0.917depressno -7.980.

Fisher's classification function for the above analysis was thus found to classify a patient as belonging to the CFS/ME group if -2.535 + 1.775 x sev_fatno + 2.889 x @50no + 1.575 x musdisno -3.274 x anxtyno -1.358 x depressno > 0 and to classify as belonging to the non-CFS/ME group otherwise i.e. if -2.535 + 1.775 x sev_fatno + 2.889 x @50no + 1.575 x musdisno -3.274 x anxtyno -1.358 x depressno < 0 .

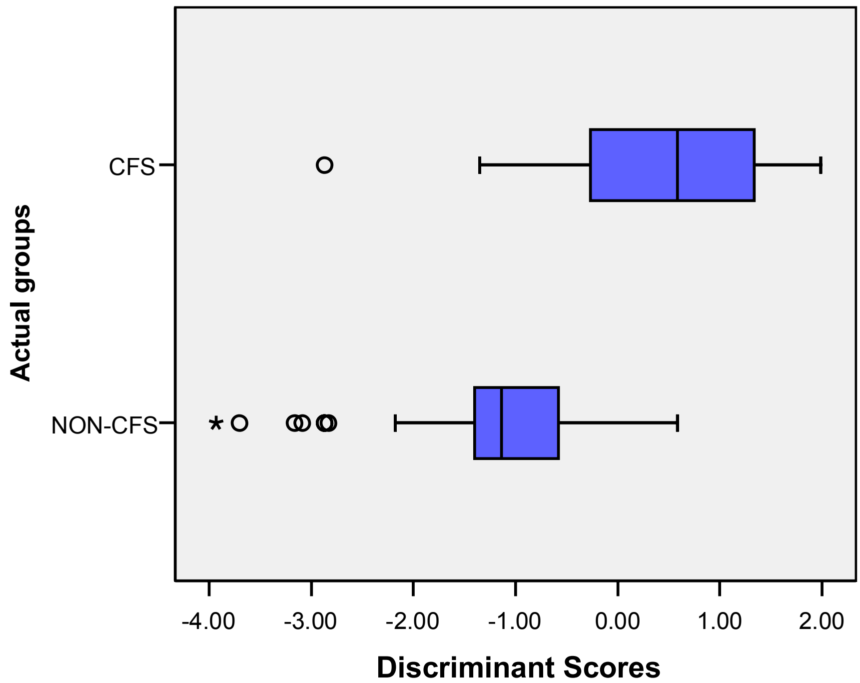


Figure 13 Box plots of discriminant scores for CFS/ME versus non-CFS/ME in the actual group

Figure 13 shows an overlap between the CFS/ME and non-CFS/ME classification in the actual groups and the presence of outliers (possibly false negatives).

Overall significance

The discriminant analysis produced only one function. Table 27 displays Eigenvalues, the percentage of variance, the cumulative percentage, and canonical correlations for the discriminant function.

Table 27 Overall model fit: Canonical Discriminant Functions Model B

Function	Eigenvalue	Percentage of Variance		Canonical Correlation	Wilks' Lambda	Chi-square	df	Sig.
		Function %	Cumulative %					
1	.726(a)	100.0	100.0	0.649	0.579	75.904	6	0.000

The Eigenvalue (ratio of the between-groups sum of squares to the within-groups sum of squares) of the discriminant function was 0.726.

The discriminant function accounted for all of the dispersion as shown by the 100% variance. The cumulative percentage of the variance explained by the discriminant function was also equal to 100%.

The measure of the association between the discriminant scores and the groups was 0.649.

Overall significance of the model

The Wilks' lambda (see Table 27) was 0.579, indicating the difference in group means. The significance value was 0.000 therefore the differences in the mean discriminant scores of the two groups were greater than could be attributed to sampling error. The significance of individual variables in dataset B derived by running discriminant analysis on each variable independent of other variables are presented in Appendix Q.

Structure matrix

The structure matrix which contains within-group correlations of each predictor variable with the discriminant function is shown in Table 28. These are listed in the order of the importance of each individual variable within the function and its importance for the predicting CFS/ME compared to the non-CFS/ME group.

Table 28 Structure Matrix Model B

	Function 1
@50no	0.471
anxtyno	-0.447
musdisno	0.339
sev_fatno	0.335
depressno	-0.251

Pooled within-groups correlations between discriminating variables and standardized canonical discriminant functions
Variables ordered by absolute size of correlation within function.

According to this matrix, the most useful variables in the discriminant function were a reduction in activity to less than 50% of the patient's premorbid activity, anxiety disorder, muscle discomfort, severe disabling fatigue affecting physical and mental functioning and depression.

Group centroids

The within-group means for the discriminant function is given in Table 29.

Table 29 Functions at Group Centroids Model B

rating of 6> =CFS/ME	Function 1
CFS/ME	0.589
non-CFS/ME	-1.216

Unstandardised canonical discriminant functions evaluated at group means

The average discriminant scores for CFS/ME and non-CFS/ME were 0.589 and -1.216 respectively for Model B.

Classification matrix of the discriminant analysis

Table 30 displays the degree of success of the classification for the model, the number and percentage of cases correctly classified and misclassified for Model B.

Table 30 Classification Results (b,c) Model B

Predicted Group Membership	Actual Group									
	Original						Cross-validated(a)			
	N			%			*N*		%	
	CFS/ ME	non-CFS/ME	Ungrouped cases	CFS /ME	non-CFS/ME	Ungrouped cases	CFS/ ME	non-CFS/ME	CFS/ ME	non-CFS/ME
CFS/ME	89	16	3	91.8	34.0	37.5	89	16	91.8	34.0
non-CFS/ME	8	31	5	8.2	66.0	62.5	8	31	8.2	66.0
Total	97	47	8	100.0	100.0	100.0	97	47	100.0	100.0

a Cross validation was done only for those cases in the analysis. In cross validation, each case was classified by the functions derived from all cases other than that case.

b 83.3% of original grouped cases correctly classified.
c 83.3% of cross-validated grouped cases correctly classified.

5.6.3. Performance of Model B

89 CFS/ME cases (91.8%) were correctly classified and 8 CFS/ME cases (8.2%) were incorrectly classified into the non-CFS/ME comparison group. The overall accuracy was 83.3% which also equalled the percentage of cross-validated cases correctly classified.

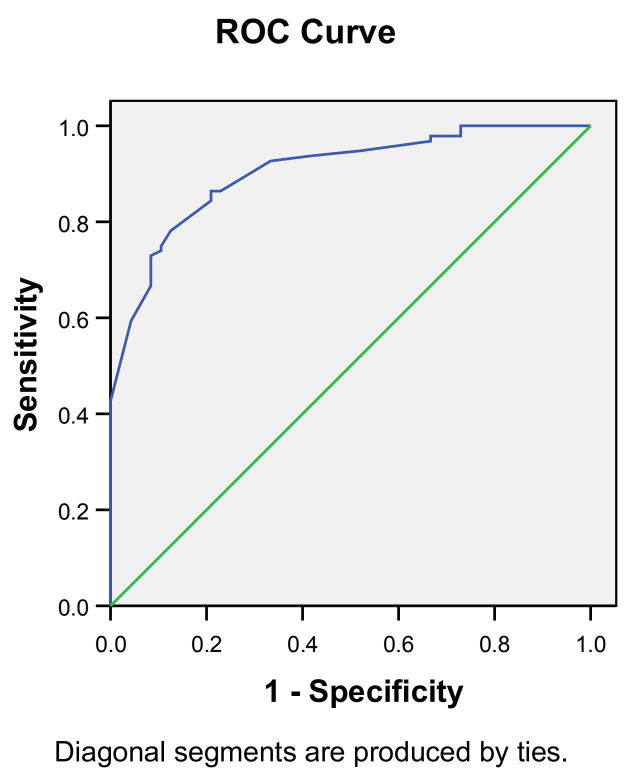


Figure 14 ***ROC Curve depicting the prediction accuracy of Model B (area under the curve= 0.905)***

Figure 14 shows that the results are fairly accurate and that the model predicts better than guessing.

The performance of the model with and without exclusionary conditions is presented in Table 31.

Table 31 Summary of the performance of Model B

Performance measures	Values (95% confidence intervals in brackets)	
	Cases with possible alternative diagnoses excluded	*Cases with possible alternative diagnoses included*
Sensitivity	0.918 (95% CI 0.864-0.956)	0.953 (95% CI 0.907-0.981)
Specificity	0.660 (95% CI 0.549-0.740)	0.468 (95% CI 0.365-0.532)
Positive predictive value	0.848 (95% CI 0.798-0.884)	0.802 (95% CI 0.763-0.826)
Negative predictive value	0.795 (95% CI 0.661-0.892)	0.815 (95% CI 0.636-0.927)
False negative rate	0.082	0.047
False positive rate	0.340	0.532
Positive likelihood ratio	2.695	1.791
Negative likelihood ratio	0.125	0.101
Overall accuracy	0.833	0.804
Kappa (p=0.000)	0.604	0.477

There was a limited effect on the sensitivity and the negative predictive value of the model when cases were excluded. However the specificity and the positive predictive values were slightly short of the confidence interval range, but improved in the model when cases were excluded. The kappa value of 0.604 indicated a substantial agreement between the actual and predicted group membership.

Validity of individual questions

When assessed independently of each other, the overall accuracy of CFS/ME predictors in order of individual importance was:

- 75.8% for a reduction in activity to less than 50% of the patient's premorbid activity
- 72.5% for severe disabling fatigue affecting physical and mental functioning
- 69.3% for muscle discomfort, painful and swollen lymph nodes, myalgia, muscle pain and multijoint pain without swelling or redness, post-exertional malaise, mild fever and generalised muscle weakness.

Results of other performance measures for individual variables are given in Table 32.

Table 32 Sensitivity, specificity, positive predictive value (PPV) and positive likelihood ratio (PLR) of CFS/ME features in cases in Model B using the reviewers' judgement as the gold standard

Clinical features	Sensitivity (%)	Specificity (%)	PPV (%)	PLR
50% decrease in activity to the premorbid activity	78.04 (69-85)	66.66 (47-82)	90.56 (83-95)	2.34 (1.39-3.91)
Muscle discomfort	78.35 (68-86)	48.93 (34-63)	76 (66-83)	1.53 (1.13-2.06)
Severe disabling fatigue affecting physical and mental functioning	93.81 (87-97)	25.53 (13-40)	72.22 (63-79)	1.25 (1.05-1.5)
Swollen lymph nodes	100 (96-100)	0 (0-7)	67.36 (59-74)	1 (1-1)
Myalgia	100 (96-100)	0 (0-7)	67.36 (59-74)	1 (1-1)
Post-exertional malaise lasting more than 24 hours	100 (96-100)	0 (0-7)	67.36 (59-74)	1 (1-1)
Muscle pain, multi joint pain without swelling or redness	100 (96-100)	0 (0-7)	67.36 (59-74)	1 (1-1)
Painful lymph nodes	100 (96-100)	0 (0-7)	67.36 (59-74)	1 (1-1)
Mild fever or chills	100 (96-100)	0 (0-7)	67.36 (59-74)	1 (1-1)
Sore throat	100 (96-100)	0 (0-7)	67.36 (59-74)	1 (1-1)

Similar to Model A, as sensitivity increased toward 100%, the proportion of cases that were classified as not having CFS/ME but who had the condition, (false negatives) decreased toward 0. With the exception of a reduction in activity to less than 50% of the patient's premorbid activity, muscle discomfort and severe disabling fatigue affecting physical and mental functioning severe pain all other criteria were uninformative (positive likelihood ratio =1) with respect to the discrimination of cases.

Summary of the discriminant analysis for Model B

Discriminant analysis for Model B thus showed that a combination of a reduction in activity to less than 50% of the patient's premorbid activity, muscle discomfort, severe disabling fatigue affecting physical and mental functioning and depression and anxiety disorder had the ability to distinguish CFS/ME from other chronic fatigue illnesses. There were no differences in the predictors of CFS/ME group membership when discriminant analysis was conducted on the dataset with and without cases having a possible alternative explanation for illness. Similar to Model A, the discriminant classifier identified an exclusionary criterion as a significant predictor of the non-CFS/ME group when all cases were included in the analysis.

III. Summary of Canonical Discriminant Functions for the model derived from the dataset with a classification threshold of 7 (Model C)

Table 33 displays the discriminant and classification function coefficients for Model C. The significant variables for this model were: a reduction in activity to less than 50% of the patient's premorbid activity (@50no), severe disabling fatigue affecting physical and mental functioning (sev_fatno), muscle discomfort (musdisno), anxiety disorder (anxtyno), generalised muscle weakness (gmusc_no) and depression (depressno). This combination distinguished best between the CFS/ME and non-CFS/ME groups for Model C.

Table 33 Discriminant and Classification Function Coefficients Model C

Independent variables	Discriminant functions		Classification functions	
	Unstandardised	Standardised	CFS/ME	non-CFS/ME
sev_fatno	1.022	0.325	8.184	6.658
@50no	1.271	0.489	4.834	2.936
musdisno	1.092	0.484	3.001	1.371
anxtyno	-1.295	-0.518	-1.911	0.022
gmusc_no	0.654	0.304	1.005	0.029
depressno	-0.915	-0.442	0.697	2.063
(Constant)	-2.252	0.325	-8.383	-5.413

Based on the results of the Table 33, the discriminant Z score formula for the model was -2.252 + 1.022 sev_fatno + 1.271@50no + 1.092 musdisno -1.295 anxtyno + 0.654 gmusc_no -0.915 depressno

The estimate of the classification function for CFS/ME cases was 8.184sev_fatno + 4.834@50no + 3.001musdisno – 1.911anxtyno + 1.005 gmusc_no + 0.697depressno - 8.383.

Fisher's classification function for the above analysis was thus found to classify a patient as belonging to the CFS/ME group if -2.97 + 1.526 x sev_fatno + 1.898 x @50no + 1.63 x musdisno -1.933 x anxtyno + 0.976 gmusc_no -1.366 x depressno > 0 and to classify

as belonging to the non-CFS/ME group otherwise i.e. if -2.97 + 1.526 x sev_fatno + 1.898 x @50no + 1.63 x musdisno -1.933 x anxtyno + 0.976 gmusc_no -1.366 x depressno < 0

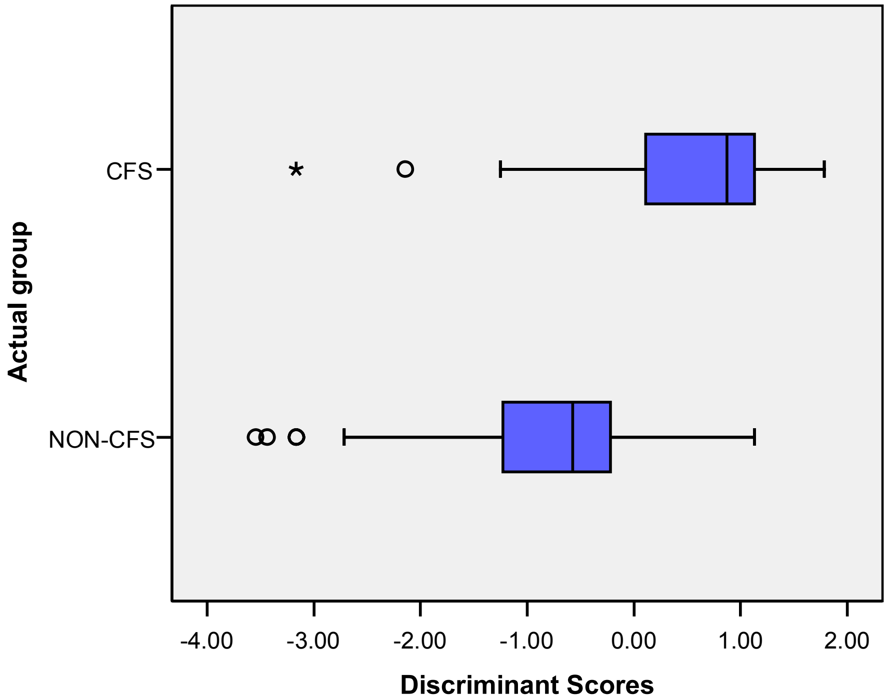


Figure 15 Box plots of discriminant scores for CFS/ME versus non-CFS/ME in the actual group

Figure 15 shows a fairly accurate classification. The presence of outliers indicates that there were a few cases which did not match the profile of the chosen group.

Overall significance

The discriminant analysis produced only one function. Table 34 displays Eigenvalues, the percentage of variance, the cumulative percentage, and canonical correlations for the discriminant function.

Table 34 Overall model fit: Canonical Discriminant Functions Model C

Function	Eigenvalue	Percentage of Variance		Canonical Correlation	Wilks' Lambda	Chi-square	df	Sig.
		Function %	Cumulative %					
1	.556(a)	100.0	100.0	0.598	0.643	61.470	6	0.000

The Eigenvalue (ratio of the between-groups sum of squares to the within-groups sum of squares) of the discriminant function was 0.556.

The discriminant function accounted for all of the dispersion as shown by the 100% variance. The cumulative percentage of the variance explained by the discriminant function was also equal to 100%. The canonical correlation (measure of the association between the discriminant scores and the groups) was 0.598.

Overall significance of the model

The Wilks' lambda (see Table 34) was 0.643 indicating that group means were different and significant at 0.000. The significance level of individual variables in dataset C, derived by running discriminant analysis on each variable independent of other variables is also presented in Appendix Q.

Structure matrix

Table 35 displays the structure matrix which contains within-group correlations of each predictor variable with the discriminant function.

Table 35 Structure Matrix Model C

	Function 1
@50no	0.485
sev_fatno	0.424
musdisno	0.416
gmusc_no	0.375
anxtyno	-0.351
depressno	-0.289

Pooled within-groups correlations between discriminating variables and standardized canonical discriminant functions
Variables ordered by absolute size of correlation within function.

According to the matrix, the most useful variables in the discriminant function were a reduction in activity to less than 50% of the patient's premorbid activity, severe disabling fatigue affecting physical and mental functioning, muscle discomfort, anxiety disorder, generalised headaches and depression.

Group centroids

The within-group means for the discriminant function is shown in Table 36.

Table 36 Functions at Group Centroids Model C

rating of 7> =CFS/ME	Function 1
CFS/ME	0.653
non-CFS/ME	-0.840

Unstandardised canonical discriminant functions evaluated at group means

Classification matrix of the discriminant analysis

Table 37 displays the degree of success of the classification for the model, the number and percentage of cases correctly classified and misclassified for Model C.

Table 37 Classification Results (b,c) Model C

	Actual Group									
Predicted Group Membership	Original						Cross-validated(a)			
	N			%			*N*		%	
	CFS/ ME	non-CFS/ME	Ungrouped cases	CFS/ ME	non-CFS/ME	Ungrouped cases	CFS/ ME	non-CFS/ME	CFS/ ME	non-CFS/ME
CFS/ME	67	19	3	82.7	30.2	37.5	64	19	79.0	30.2
non-CFS/ME	14	44	5	17.3	69.8	62.5	17	44	21.0	69.8
Total	81	63	8	100.0	100.0	100.0	81	63	100.0	100.0

a Cross validation was done only for those cases in the analysis. In cross validation, each case was classified by the functions derived from all cases other than that case.
b 77.1% of original grouped cases correctly classified.
c 75.0% of cross-validated grouped cases correctly classified.

5.6.4. Performance of Model C

Performance of the case-definition algorithm

The overall accuracy of classification was 77.1%, whilst the percentage of cross-validated cases correctly classified was 75.0%. 67 CFS/ME cases (82.7%) were correctly classified and 14 of the CFS/ME cases (17.3%) were incorrectly classified as non-CFS/ME.

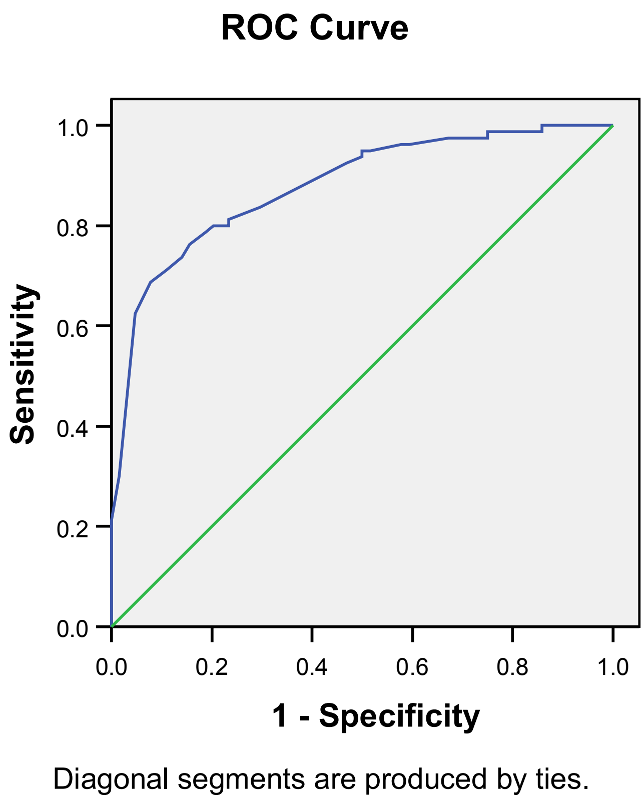


Figure 16 ROC Curve for Model C (area under the curve= 0.879)

Figure 16 shows that the results are fairly accurate and that the model predicts better than guessing.

The performance of the model with and without exclusionary conditions is presented in Table 38.

Table 38 Summary of the performance of Model C

Performance measures	Values (95% confidence intervals in brackets)	
	Cases with possible alternative diagnoses excluded	*Cases with possible alternative diagnoses included*
Sensitivity	0.827 (95% CI 0.755-0.886)	0.869 (95% CI 0.799-0.923)
Specificity	0.698 (95% CI 0.605-0.774)	0.594 (95% CI 0.509-0.660)
Positive predictive value	0.779 (95% CI 0.711-0.834)	0.723 (95% CI 0.664-0.768)
Negative predictive value	0.759 (95% CI 0.657-0.840)	0.788 (95% CI 0.675-0.876)
False negative rate	0.172	0.131
False positive rate	0.301	0.405
Positive likelihood ratio	2.742	2.141
Negative likelihood ratio	0.247	0.220
Overall accuracy	0.771	0.745
Kappa (p=0.000)	0.530	0.474

There was a limited effect on the sensitivity and the negative predictive value of the model when cases were excluded. Similar to Model B, the specificity and the positive predictive values were slightly short of the confidence interval range but improved in the model when cases were excluded. The overall level of accuracy was the same in both. The kappa value of 0.530 indicated moderate agreement between the actual and predicted group membership.

Validity of individual questions

When assessed independently of each other, each of the following CFS/ME predictor variables (in order of overall accuracy) discriminated between CFS/ME cases and the non-CFS/ME comparison group to an extent:

- A reduction in activity to less than 50% of the patient's premorbid activity - 65.4%
- Generalised muscle weakness- 64.1%
- Severe disabling fatigue affecting physical and mental functioning and post-exertional malaise- 63.4%
- Muscle discomfort- 62.1%
- Generalised headaches- 60.8%
- Prolonged generalised fatigue from levels of exercise easily tolerated in the premorbid state- 59.5%

- Mild fever- 58.2%
- Swollen lymph nodes- 54.9%.

Results of other performance measures for individual variables are given in Table 39.

Table 39 Sensitivity, specificity, positive predictive value (PPV) and positive likelihood ratio (PLR) of CFS/ME features in cases in Model D using the reviewers' judgement as the gold standard

Clinical features	Sensitivity (%)	Specificity (%)	PPV (%)	PLR
Severe disabling fatigue affecting physical and mental functioning	96.29 (89-99)	23.8 (13-36)	61.9 (52-70)	1.26 (1.09-1.46)
50% decrease in activity from premorbid activity	91.35 (83-96)	36.5 (24-49)	64.91 (55-73)	1.43 (1.17-1.75)
Prolonged generalised fatigue from exercise	88.88 (79-94)	23.8 (13-36)	60 (50-68)	1.16 (0.99-1.36)
Post-exertional malaise lasting more than 24 hours	83.95 (74-91)	38.09 (26-51)	63.55 (53-72)	1.35 (1.09-1.68)
Muscle discomfort	81.48 (71-89)	46.03 (33-59)	66 (55-75)	1.5 (1.17-1.93)
Muscle pain, multi joint pain without swelling or redness	80.24 (69-88)	38.09 (26-51)	62.5 (52-71)	1.29 (1.03-1.61)
Myalgia	79.01 (68-87)	39.68 (27-52)	62.74 (52-72)	1.3 (1.04-1.64)
Unexplained generalised muscle weakness	75.3 (64-84)	50.79 (37-63)	66.3 (55-75)	1.53 (1.15-2.02)
Generalised headaches (different from the premorbid state)	55.55 (44-66)	66.66 (53-78)	68.18 (55-79)	1.66 (1.11-2.48)
Mild fever or chills	45.67 (34-57)	73.01 (60-83)	68.51 (54-80)	1.69 (1.05-2.7)
Swollen lymph nodes	100 (95-100)	0 (0-5)	56.25 (47-64)	1 (1-1)

With the exception of swollen lymph nodes (positive likelihood ratio= 1), all other criteria on an individual basis were useful in the discrimination of cases. The least sensitive but most specific criteria were unexplained generalised muscle weakness, generalised headaches and mild fever or chills. Specificity was low in the other criteria.

Summary of the discriminant analysis for Model C

The discriminant analysis for Model C thus showed that a combination of a reduction in activity to less than 50% of the patient's premorbid activity, severe disabling fatigue affecting physical and mental functioning, muscle discomfort, anxiety disorder,

generalised muscle weakness and depression had the ability to distinguish CFS/ME from other chronic fatigue illnesses.

The only difference noticed when discriminant analysis was conducted on the dataset with cases having a possible alternative explanation for illness was that the symptom of generalised headaches was included as a significant predictor of the CFS/ME group instead of generalised muscle weakness and multiple chemical sensitivity (an overlapping syndrome) was identified as a significant predictor of the non-CFS/ME group.

IV. Summary of Canonical Discriminant Functions for the model derived from the dataset with a classification threshold of 8 (Model D)

Table 40 displays the discriminant and classification function coefficients for the last model. The combination which distinguished best between the CFS/ME and non-CFS/ME groups for Model D was composed of a reduction in activity to less than 50% of the patient's premorbid activity (@50no), swollen lymph nodes (swoll_no), myalgia (myalgno), anxiety disorder (anxtyno), generalized muscle weakness (gmusc_no), depression (depressno), migratory arthralgia (migartno), hypothyroidism (hypothyno) and fibromyalgia syndrome (FMS_no).

Table 40 Discriminant and Classification Function Coefficients Model D

	Discriminant functions		Classification functions	
Independent variabl	Unstandardised	Standardised	CFS/ME	non-CFS/ME
@50no	0.896	0.348	5.670	3.988
myalgno	1.211	0.530	5.255	2.983
anxtyno	-1.105	-0.442	-1.987	0.086
swoll_no	0.869	0.281	2.095	0.464
hypothyno	-1.509	-0.441	-2.672	0.160
gmusc_no	0.975	0.455	2.993	1.164
migartno	0.742	0.350	0.354	-1.039
depressno	-0.638	-0.310	0.538	1.735
FMS_no	-1.289	-0.519	-2.047	0.373
(Constant)	-1.537		-7.520	-3.576

From the Table above, the discriminant Z score for Model D was -1.537 + 0.896@50no + 1.211 myalgno -1.105anxtyno + 0.869swoll_no -1.509hypothyno + 0.975gmusc_no + 0.742migartno -0.638depressno -1.289FMS_no

The estimate of the classification function for CFS/ME cases was 5.670@50no + 5.255myalgno -1.987anxtyno + 2.095swoll_no -2.672hypothyno + 2.993gmusc_no + 0.354migartno + 0.538depressno -2.047FMS_no - 7.520.

Fisher's classification function for the above analysis was thus found to classify a patient as belonging to the CFS/ME group if -3.944 + 1.682 x @50no + 2.272 x myalgno -2.073 x anxtyno + 1.631 x swoll_no -2.832 x hypothyno + 1.829 x gmusc_no + 1.393 x migartno -1.197 x depressno -2.42 x FMS_no > 0, and to classify as belonging to the non-CFS/ME group otherwise i.e. if -3.944 + 1.682 x @50no + 2.272 x myalgno -2.073 x anxtyno + 1.631 x swoll_no -2.832 x hypothyno + 1.829 x gmusc_no + 1.393 x migartno -1.197 x depressno -2.42 x FMS_no < 0.

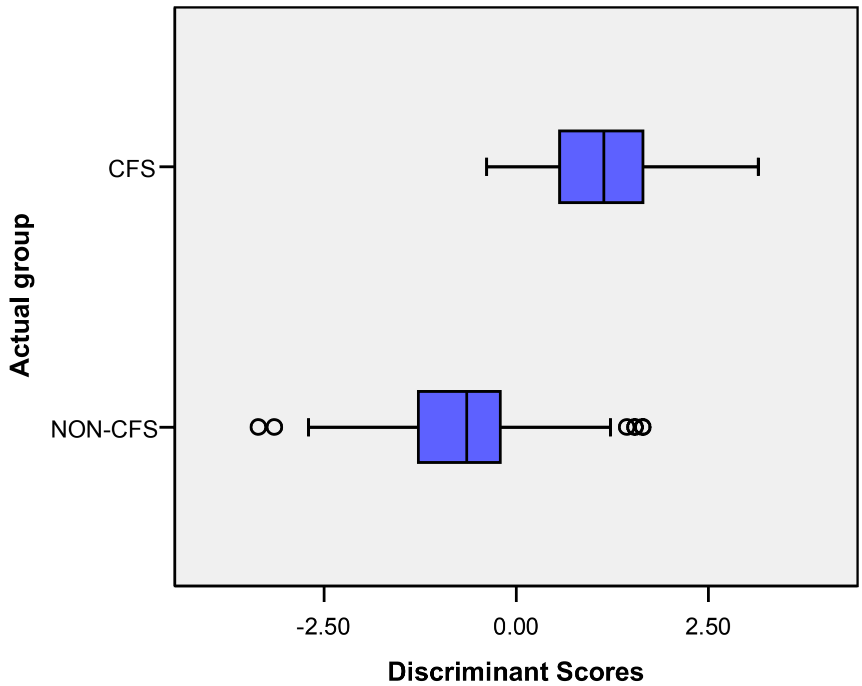


Figure 17 Box plots of discriminant scores for CFS/ME versus non-CFS/ME in the actual group

Figure 17 shows an accurate classification of the CFS/ME cases in the actual group and a less accurately classified non-CFS/ME comparison group (outliers are possibly false negatives) in the actual group.

Overall significance

Similar to the other models, the discriminant analysis of subset D produced only one function.

Table 41 displays Eigenvalues, the percentage of variance, the cumulative percentage, and canonical correlations for the discriminant function.

Table 41 Overall model fit: Canonical Discriminant Functions Model D

Function	Eigenvalue	Percentage of Variance		Canonical Correlation	Wilks' Lambda	Chi-square	df	Sig.
		Function %	Cumulative %					
1	.824(a)	100.0	100.0	0.672	0.548	82.642	9	0.000

The Eigenvalue of the discriminant function as shown in the above table was 0.824. The function accounted for all of the dispersion (% of variance =100%).
The cumulative percentage of the variance explained by the function was also equal to 100%. The canonical correlation was 0.672.

Overall significance of the model

The Wilks' lambda (see Table 41) was 0.548 indicating a difference in the group means. The significance value was 0.000.
The significance of individual variables in dataset D derived by running discriminant analysis on each variable independent of other variables was also computed and are presented in Appendix Q.

Structure matrix

Table 42 displays the structure matrix which contains within-group correlations of each predictor variable with the discriminant function.

Table 42 Structure Matrix Model D

	Function 1
@50no	0.365
myalgno	0.336
gmusc_no	0.302
anxtyno	-0.288
swoll_no	0.273
migartno	0.267
hypothyno	-0.222
depressno	-0.200
FMS_no	-0.192

Pooled within-groups correlations between discriminating variables and standardized canonical discriminant functions
Variables ordered by absolute size of correlation within function.

According to the matrix, the most useful variables in the discriminant function were myalgia, a reduction in activity to less than 50% of the patient's premorbid activity, unexplained generalized muscle weakness, swollen lymph nodes, migratory arthralgia and anxiety disorder.

Group centroids

Table 43 displays the group centroids.

Table 43 Functions at Group Centroids Model D

rating of 8> =CFS/ME	Function 1
CFS/ME	1.199
non-CFS/ME	-0.678

Unstandardised canonical discriminant functions evaluated at group means

The average discriminant scores for CFS/ME and non-CFS/ME were 1.199 and -0.678 respectively.

Classification matrix of the discriminant analysis

Table 44 displays the degree of success of the classification for the model, the number and percentage of cases correctly classified and misclassified for Model D.

Table 44 Classification Results (b,c) Model D

Predicted Group Membership	Actual group									
	Original						Cross-validated(a)			
	N			%			*N*		%	
	CFS/ ME	non-CFS/ME	Ungrouped cases	CFS/ ME	non-CFS/ME	Ungrouped cases	CFS/ ME	non-CFS/ME	CFS/ ME	non-CFS/ME
CFS/ME	40	11	2	76.9	12.0	25.0	34	12	65.4	13.0
non-CFS/ME	12	81	6	23.1	88.0	75.0	18	80	34.6	87.0
Total	52	92	8	100.0	100.0	100.0	52	92	100.0	100.0

a Cross validation was done only for those cases in the analysis. In cross validation, each case was classified by the functions derived from all cases other than that case.
b 84.0% of original grouped cases were correctly classified.
c 79.2% of cross-validated grouped cases were correctly classified.

5.6.5. Performance of Model D

Performance of the case-definition algorithm

40 CFS/ME cases (76.9%) were correctly classified and 12 CFS/ME cases (23.1%) were incorrectly classified as non-CFS/ME. The overall accuracy was 84.0% whilst the percentage of cross-validated cases correctly classified was 79.2%.

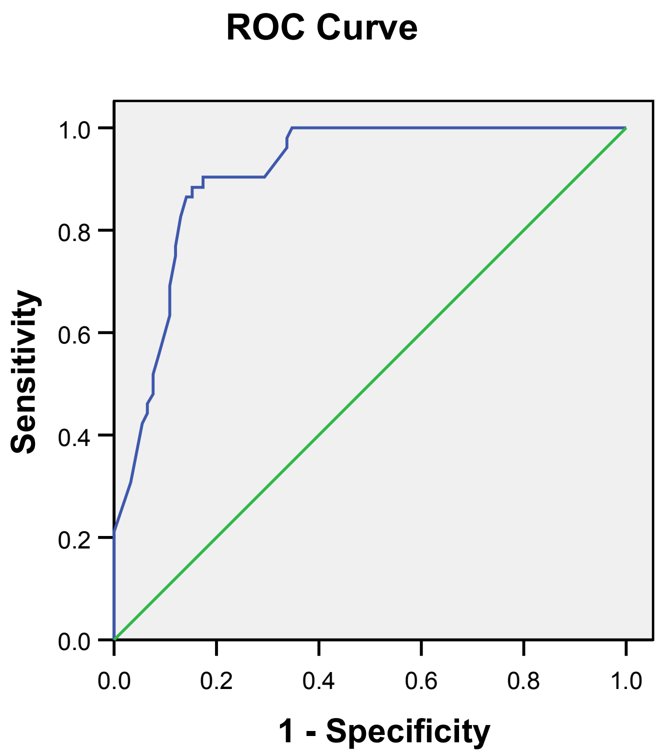


Figure 18 ROC curve for Model D showing that the model predicts well (area under curve= 0.911)

Figure 18 shows the effect of the increase in the threshold level. The results are still fairly accurate.

The performance of the case-definition algorithm is summarised in Table 45.

Table 45 Summary of the performance of Model D

Performance measures	Values (95% confidence intervals in bracket)	
	Cases with possible alternative diagnoses excluded	*Cases with possible alternative diagnoses included*
Sensitivity	0.769 (95% CI 0.666-0.847)	0.704 (95% CI 0.600-0.785)
Specificity	0.880 (95% CI 0.822-0.924)	0.879 (95% CI 0.822-0.923)
Positive predictive value	0.784 (95% CI 0.679-0.864)	0.760 (95% CI 0.647-0.848)
Negative predictive value	0.871 (95% CI 0.813-0.915)	0.845 (95% CI 0.790-0.887)
False negative rate	0.230	0.296
False positive rate	0.119	0.121
Positive likelihood ratio	6.433	5.801
Negative likelihood ratio	0.262	0.337
Overall accuracy	0.840	0.817
Kappa (p=0.000)	0.652	0.592

The results show that impact of excluding cases with possible alternative diagnoses was limited as values remained within the 95% confidence interval range. In contrast to Model A, sensitivity and specificity values decreased when cases were not excluded from the analysis.

The kappa value of 0.652 indicated substantial agreement between the actual and predicted group membership.

Validity of individual questions

When assessed independently, some variables demonstrated an ability to discriminate to an extent. There was an increase in the number and variability of the predictors in Model D compared to the former models. The predictors included symptoms associated with inflammatory or immune processes and cognitive dysfunction.

The overall accuracy of individual variables was:

- Swollen lymph nodes - 68.6%
- Painful cervical lymph nodes- 66.7%
- Hypersensitivity to noise-65.4%
- Orthostatic intolerance- 68.6%

The following variables had an overall accuracy of 64.7%:

- Migratory arthralgia without joint swelling or redness
- A reduction in activity to less than 50% of the patient’s premorbid activity
- Infection at onset
- Generalised headaches
- Muscle discomfort
- Myalgia
- Post-exertional malaise
- Heat and cold intolerance
- Generalised fatigue from levels of exercise easily tolerated in premorbid state impaired memory or concentration
- Muscle pain, muscle & multi-joint pain without swelling or redness
- Generalized muscle weakness
- Difficulty thinking
- Mild fever or chills.

The performance of relevant individual variables is presented in Table 46.

Table 46 Sensitivity, specificity, positive predictive value (PPV) and positive likelihood ratio (PLR) of CFS/ME features in cases in Model D using the reviewers' judgement as the gold standard

Clinical features	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**PLR (%)**
Generalised headaches	63.46 (48-76)	64.13 (53-73)	50 (37-62)	1.76 (1.25-2.49)
Migratory arthralgia without joint swelling or redness	51.92 (37-65)	71.73 (61-80)	50.94 (36-64)	1.83 (1.21-2.78)
Hypersensitivity to noise	44.23 (30-58)	78.26 (68-86)	53.48 (37-68)	2.03 (1.24-3.33)
Infection at onset & laboratory evidence	34.61 (21-49)	83.69 (74-90)	54.54 (36-71)	2.12 (1.17-3.84)
Loss of thermostatic ability or other neuroendocrine manifestation	30.76 (18-45)	84.78 (75-91)	53.33 (34-71)	2.02 (1.07-3.8)
Painful lymph nodes	28.84 (17-43)	89.13 (80-94)	60 (38-78)	2.65 (1.28-5.47)
Orthostatic intolerance/other autonomic manifestation	25 (14-38)	92.39 (84-96)	65 (40-84)	3.28 (1.39-7.71)
Swollen lymph nodes	23.07 (12-36)	66.66 (40-86)	93.47 (86-97)	3.53 (1.41-8.87)
Mild fever or chills	0 (0-6)	100 (96-100)	-	-
Substantial impairment in short-term memory	0 (0-6)	100 (96-100)	-	-
50% decrease in activity from premorbid	0 (0-3)	100 (93-100)	-	-
Severe disabling fatigue affecting physical and mental functioning	0 (0-3)	100 (93-100)	-	-
Muscle discomfort	0 (0-3)	100 (93-100)	-	-
Myalgia	0 (0-3)	100 (93-100)	-	-
Post-exertional malaise	0 (0-3)	100 (93-100)	-	-
Unexplained generalised muscle weakness	0 (0-3)	100 (93-100)	-	-
Prolonged generalised fatigue from exercise easily tolerated in the patient's premorbid state	0 (0-3)	100 (93-100)	-	-
Muscle pain, multi-joint pain without swelling or redness	0 (0-3)	100 (93-100)	-	-

The variables which demonstrated individual discriminant ability in this model were generalised headaches, migratory arthralgia without joint swelling or redness, hypersensitivity to noise, infection at onset & laboratory evidence, neuroendocrine manifestation, painful lymph nodes, orthostatic intolerance/other autonomic manifestation and swollen lymph nodes.

Summary of the discriminant analysis for Model D

The discriminant analysis thus selected the combination of the strongest predictor variables for Model D. These are myalgia, a reduction in activity to less than 50% of the patient's premorbid activity, unexplained generalized muscle weakness,

swollen lymph nodes, migratory arthralgia and anxiety disorder. The remaining variables were not included in the statistical model.

5.6.6. Comparison of the discriminant and summary performance measures

A summary of the results of the discriminant analysis and classification accuracy of the models are presented in Tables 47, 48 and 49.

Table 47 Predictor variables classifying cases into the CFS/ME group

Variables	Models			
	A	B	C	D
Fifty percent (50%) decrease in activity compared to the premorbid state (functional impairment)	X	X	X	X
Severe debilitating fatigue affecting physical and mental functioning (fatigue, neuro physiological and psychological symptoms)	X	X	X	-
Muscle discomfort/Myalgia (pain and musculoskeletal symptoms)	X	X	X	X
Generalised muscle weakness or headaches	-	-	X	X
Migratory arthralgia (musculoskeletal symptoms)	-	-	-	X
Swollen lymph nodes	-	-	-	X

The analysis demonstrated that a reduction in activity to less than 50% of the patient's premorbid activity (an indicator of functional impairment) explained the most variance in group membership and was thus a major predictor of CFS/ME across all models. Other predictors for models A, B and C were severe debilitating fatigue affecting physical and mental functioning (fatigue symptoms) and muscle discomfort (muscular skeletal symptoms).

The selection of symptoms of generalised muscle weakness (or headaches), migratory arthralgia, swollen lymph nodes and myalgia at higher thresholds (subsets C and mainly D) may be indicative of more severe cases within the illness construct or a different phase of the illness. This may also allow an accurate characterisation of possible subtypes of the syndrome.

Table 48 Predictor variables classifying cases into the non-CFS/ME group

Variables	Models			
	A	B	C	D
Anxiety disorder (psychiatric co morbidity)	X	X	X	X
Depression (psychiatric co morbidity)	-	X	X	X
Hypothyroidism (co morbidity/ exclusionary condition)	-	-	-	X
Fibromyalgia syndrome (overlapping syndrome)	-	-	-	X

At the highest threshold level (model D), CFS/ME cases appeared to be more distinct from overlapping syndromes and comorbidities as cases with fibromyalgia syndrome, hypothyroidism, anxiety disorder and depression were classed as part of non-CFS/ME group.

Performance measures

Threshold dependent and independent measures were used to assess the performance of the models as described further on.

Threshold dependent measures

The summary measures of performance of each model were calculated at the different threshold or cut-off values and are presented in Table 49 below.

Table 49   Comparison of performance measures for the CFS/ME case-definition model

Model summaries	A	B	C	D
Sensitivity (true positive rate)	0.945	0.918	0.827	0.769
Specificity (true negative rate)	0.571	0.660	0.698	0.880
Positive predictive value	0.873	0.848	0.779	0.784
Negative predictive value	0.769	0.795	0.759	0.871
False negative rate	0.055	0.082	0.172	0.230
False positive rate	0.428	0.340	0.301	0.119
Positive likelihood ratio	2.204	2.695	2.742	6.433
Negative likelihood ratio	0.096	0.125	0.247	0.262
Overall accuracy	0.854	0.833	0.771	0.840
Kappa (p=0.000)	0.566	0.604	0.530	0.652

Highest values indicated by shaded boxes

The results from the sensitivity analysis summarized in Table 49, indicate that the models performed well with an overall accuracy ranging from approximately 77% to 85 %. Assuming the study objective was to develop an epidemiological case-definition that gave maximum overall accuracy, i.e. not specifically taking into account the sensitivity or specificity; the results show that Model A would probably be the best for the case-definition algorithm. This is because it had the highest overall accuracy at 85.4%.

Model A also had the highest sensitivity (94.5%) but the lowest specificity at 57.1%. Models A and B produced the highest positive predictive values. On the other hand, Model D had the highest negative predictive value and false negative rate.

With increasing threshold, (from Model A to D) it can be noted that the positive likelihood ratio also increases. Models A, B, C have moderate probabilities (2.204, 2.695 and 2.742 respectively) but the most significant likelihood ratio of 6.433 was recorded for Model D. Kappa as a measure of improvement over chance classification had statistically significant values that ranged from moderate to substantial agreement at p=0.000. The kappa value fell when the size of one class far exceeded the other.

The changes in sensitivity and specificity across the models can be observed in the graph in Figure 19. The pattern of differences in these measures may be as a result of the subjective nature of assignment of threshold levels or the prevalence of the resulting dependent variable in each model (Hosmer, Lemeshow 1989).

For example, Model A which had a threshold of five (5), had the highest proportion of CFS/ME cases (75.7%) and the lowest proportion of non-CFS/ME (25.3%) and thus a high model sensitivity when the response variable (CFS/ME cases) was common or highly prevalent. Conversely, Model D which had a threshold level of eight (8), had the lowest proportion of CFS/ME cases (36.1%) and highest proportion of non-CFS/ME (63.9%), thus a low model sensitivity when the response variable (CFS/ME cases) was rare or low in prevalence. It can thus be inferred that there exists possible threshold effects in the performance measures.

The 'threshold effect' is a common cause of heterogeneity in test accuracy which arises when differences in sensitivities and specificities or likelihood ratios occur

due to different cut-offs or thresholds used to define a positive (or negative) test result (Zamora et al. 2006).

As described earlier, an impact of the threshold effect was the negative correlation between sensitivities and specificities (or a positive correlation between sensitivities and 1-specificities).

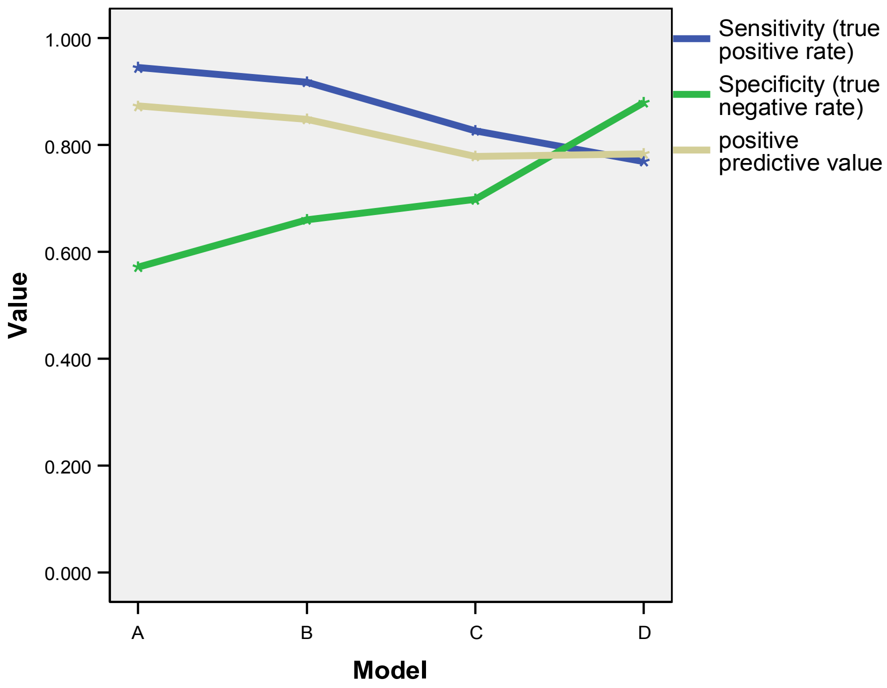


Figure 19 Summary measures of the performance of each model

As observed in the top graph of Figure 19, sensitivity decreased consistently whilst specificity increased from Model A to D.

Threshold independent measures

Following the work by Kaur and Ragahva (2004), a threshold independent measure the AUC, (area under the curve) based on a graphical plot of a receiver operating characteristic (ROC) curve, was used to judge the performance of the four models (Kaur, Raghava 2004).

The ROC method compared the discriminating power of each of the four models in the prediction of persons with CFS/ME in order to determine the best model for the

epidemiological case-definition. This was achieved by plotting a graph of sensitivity against the false-positive rate (1-specificity) for the different threshold values of the models (Hanley, McNeil 1982). Four ROC curves were generated and compared against each other, one for each model and plotted on the graph shown in Figure 20.

The four models produced AUC values greater than 0.5 (above the diagonal line on the ROC curve), indicating that they, were better than relying on pure chance, and that they had a reasonable ability to discriminate between persons with and without CFS/ME. The ROC curve with the best performance was judged to be the one that was highest and lay farthest to the left of the ROC space since this provided the greatest balance between sensitivity and specificity (SPSS 2005).

Figure 20 shows the ROC curves for the four models. There is some overlap at different points and Models A, B and C are clearly separated from Model D. Models B and C appear almost identical.

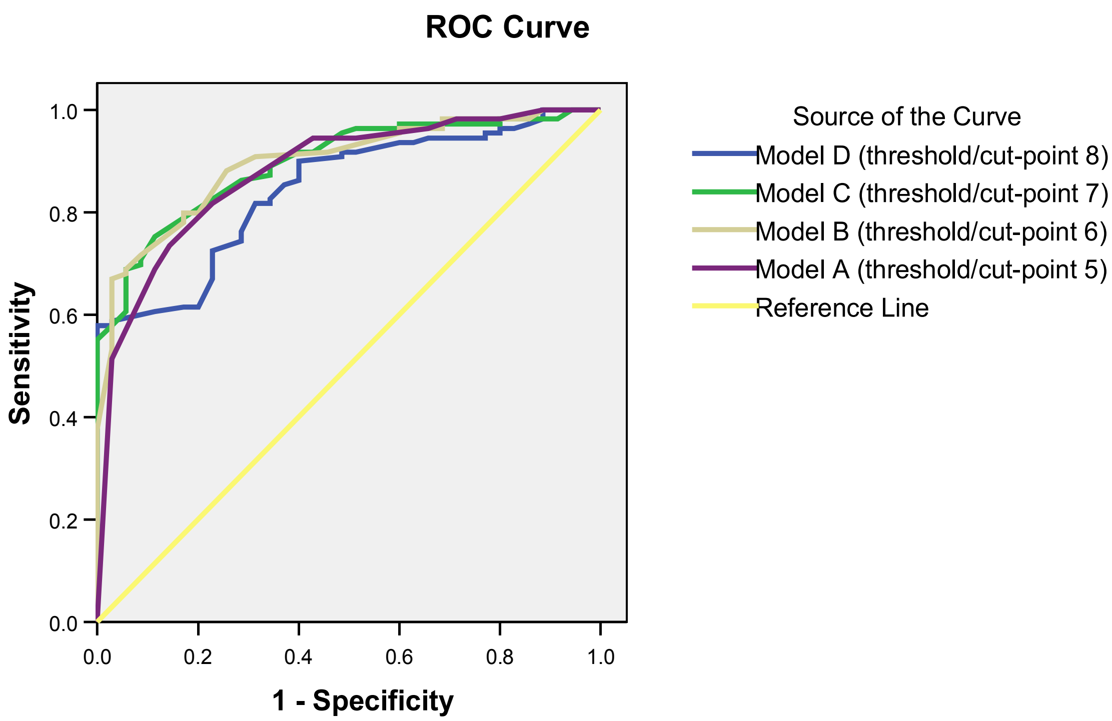


Figure 20 ROC curves describing the discrimination of the probabilities obtained from the discriminant analysis for how well the four models predicted CFS/ME. Estimates of the areas under each curve are shown. Based on their distances from the reference line, all four models did better than guessing.

The results of this visual exploration of accuracy measures displayed by the ROC curves for the four models, suggests the possibility of the presence of heterogeneity within CFS/ME particularly between the first three models (Models A, B and C) and Model D. This was noted earlier in the summary results of the discriminant analysis (Tables 47 and 48), that the features for Models A, B and C were fairly identical but differed from Model D.

The variations in the accuracy estimates amongst the two possible subtypes may be due to chance as well as variations in study population (e.g. severity of disease and co-morbidities) (Zamora et al. 2006). Therefore to assess further the variations between the two subtypes, as well as the best model for predicting CFS/ME, the significance level of the models produced during the ROC curve analysis were assessed (Park, Goo & Jo 2004).

Model B correctly classified a higher percentage of CFS/ME cases compared to Model C with relatively good sensitivity. Model B also had the largest AUC of the four models as shown in Table 50 below, which indicates the best overall performance (stated previously).

Table 50 Area under the Curve for Models A, B, C and D

Test Result Variable(s)	Area	Std. Error(a)	Asymptotic Sig.(b)	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
Model A	0.878	0.032	0.000	0.815	0.941
Model B	0.896	0.027	0.000	0.843	0.949
Model C	0.895	0.027	0.000	0.843	0.947
Model D	0.844	0.033	0.000	0.779	0.909

a Under the nonparametric assumption
b Null hypothesis: true area = 0.5

Thus from these results Model B was deemed to be the best model. This choice is in accordance with the main aim of the study i.e. to develop a case-definition that can differentiate CFS/ME from other cases of chronic fatigue and that can also be used for surveillance purposes or population health needs assessment.

Table 50 also showed that there is little difference between the AUC values for Models B and C, thus suggesting that they are reasonably homogenous and that there is no substantial heterogeneity with Model A. It also reflects the significance level of the four models which is less than 0.05, (i.e. better than guessing). It can therefore be inferred that whilst any existing variations in accuracy between Models A, B and C may attributed to threshold effect, any variations in the accuracy estimates amongst the two subtypes is more likely as a result of variations in the study population rather than chance.

5.7. Case-definition building summary

The previous sections tested the associations between individual variables and the CFS/ME group to determine the criteria to be included in the final case-definition model. They generated a symptom list for predicting CFS/ME as a whole using SBV, and also determined the combination of variables that differentially predicted CFS/ME and non-CFS/ME cases within the specified groups. It was also possible to assess the variables independent of the group combination (i.e. individual variables were entered into the discriminant analyses).

In comparing the SBV technique with classical discriminant analysis, it was found that generally, the performance values obtained from the SBV models though they indicated reasonably accurate measures, were lower compared to those obtained during the discriminant analysis for the same model category. They were also lower compared to those obtained during ROC curve analysis (AUC) for the same model category. However using SBV, it was possible to quantify the set of questions from a list of variables demonstrating a significant relationship with the CFS/ME group (refer to section 5.4.1), that could discriminate between CFS/ME cases and the non-CFS/ME comparison group. It was thus possible to assess the effect of the cut point on the performance of the model.

Unlike the discriminant analysis which specified the most useful variables contributing to the function, the SBV was less specific. On application of the SBV, any of the variables stood an equal chance of being selected thus there was possibility of excluding highly relevant variables from the decision rule.

A summary of the statistical results and performance of each model based on the discriminant analysis (including the ROC analysis), the SBV technique are given in Table 51.

Table 51 Summary table of the epidemiological case-definition performance measures

	Levels/datasets			
	I/A	II/B	III/C	IV/D
Classification threshold	5	6	7	8
Number of cases				
CFS/ME	109	97	81	52
Non-CFS/ME	35	47	63	92
Percentage total				
CFS/ME	75.7	67.4	56.3	36.1
Non-CFS/ME	24.3	32.6	43.7	63.9
Sum of binary variables				
Minimum number of variables required for CFS/ME classification	6	7	9	10
Overall accuracy	80.5	75.2	74.5	71.9
Sensitivity or % CFS/ME correctly classified (true positives)	89.8	84.8	77.1	70.4
Specificity or % non-CFS/ME correctly classified (true negatives)	50.0	54.2	71.4	72.7
Classical discriminant analysis				
Overall accuracy	85.4	83.3	77.1	84.0
Sensitivity or % CFS/ME correctly classified (true positives)	94.5	91.8	82.7	76.9
Specificity or % non-CFS/ME correctly classified (true negatives)	57.1	66.0	69.8	88.0
Positive predictive value	0.873	0.848	0.779	0.784
Negative predictive value	0.769	0.795	0.759	0.871
False negative rate	0.055	0.082	0.172	0.230
False positive rate	0.428	0.340	0.301	0.119
Positive likelihood ratio	2.204	2.695	2.742	6.433
Negative likelihood ratio	0.096	0.125	0.247	0.262
Kappa (p=0.000)	0.566	0.604	0.530	0.652
Area under the ROC curve	87.8	89.6	89.5	84.4

The classification rules for the final models incorporated the results of the all statistical methods employed for discrimination as described in previous sections. The rules were constructed at the four threshold levels for the models assessed in this study. They are presented as the mandatory and supportive criteria that identify a case of CFS/ME.

(i) Step 1 (Mandatory criteria)

The first step in defining the classification rules or criteria, involved identifying the combination of predictor variables that were derived from the discriminant analysis. These formed the mandatory criteria. All variables in this category were required for the

classification rules. Although the performance of the discriminant analysis and the SBV models were comparable i.e. they both produced models with fairly good accuracy, the discriminant analysis performed better than the SBV across the four thresholds in terms of sensitivity, specificity and accuracy.

Further, the discriminant analysis procedure showed which core symptoms were the most important for identifying CFS/ME in patients presenting with unexplained chronic fatigue of at least six months. It also differentiated the features that did not contribute substantially to the discriminant model. As the discriminant analysis showed a better performance, it was decided that this was the more valid and reliable way of correctly classifying CFS/ME cases. Exclusion criteria derived from the discriminant analysis were also listed.

(ii) Step 2 (Supportive criteria)

A limitation of the discriminant analytic approach to the development of the case-definition was that some symptoms were highly prevalent in both CFS/ME and non-CFS/ME groups and thus did not have the required discriminative ability. In order to avoid limiting the applicability of the findings, the results of other analytic procedures carried out in this study were also considered.

Therefore, the second step in defining the classification rules was to assess not only the variables that were highly prevalent in each dataset and/or demonstrated a statistically significant association with the CFS/ME group but also those that demonstrated the required individual discriminative ability.

The supportive criteria were thus based on the SBV analysis and formed the remainder of the variables that were included in the discriminant analysis but did not emerge as significant predictors within the group membership (and thus did not form part of the mandatory criteria).

The minimum number of supportive criteria required to produce a reasonably accurate classification was determined by the results of the SBV as this produced reasonable estimates based on the number of positive responses. The number required

for the supportive criteria was also the remainder after the number of mandatory criteria had been subtracted.

Each criterion was placed into a broader group category described under the section on SBV (section 5.5). The categories which had at least two criteria were: symptoms of exertion intolerance (2 variables), musculoskeletal symptoms (3 variables), neurocognitive symptoms (3 variables), immune symptoms (3 variables) and symptoms of reduced functional or mental capacity (3 variables).

(iii) Step 3

Following a brief review of the four classification rules, only one classification rule was specifically aimed at the outcome measure of the study. Therefore the third step in defining the final classification rule for CFS/ME included the results of the ROC curve (AUC) procedure. This approach clearly identified the model on which to base the classification rule for the purpose of case-definition of CFS/ME in the study context.

The selection of this model took into account:

- The subjective nature of the threshold levels used to construct the models
- The relative importance of accuracy and sensitivity versus specificity in the discriminant analysis and SBV methods
- The prevalence of independent variables in the sample and the models performance as assessed by the receiver-operating characteristic (ROC) curve which is a threshold independent method, thought to be more objective and robust than other methods (as described in section 5.5.6).

Table 52 shows the different classification rules for CFS/ME, the mandatory and supportive criteria and the exclusionary conditions according to the four models.

Table 52 Summary of the CFS/ME classification rules

<table>
<tr><th>Method</th><th>Model A</th><th>Model B</th><th>Model C</th><th>Model D</th></tr>
<tr><td>Minimum criteria required (SBV) and symptom group</td><td>At least six (6) required</td><td>At least seven (7) required</td><td>At least nine (9) required</td><td>At least ten (10) required</td></tr>
<tr><td>Mandatory criteria (DA)</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Reduced functional or mental capacity</td><td>reduction in activity to less than 50% of the patient’s premorbid activity
Severe debilitating fatigue affecting physical and mental functioning</td><td>reduction in activity to less than 50% of the patient’s premorbid activity
Severe debilitating fatigue affecting physical and mental functioning</td><td>reduction in activity to less than 50% of the patient’s premorbid activity
Severe debilitating fatigue affecting physical and mental functioning</td><td>reduction in activity to less than 50% of the patient’s premorbid activity</td></tr>
<tr><td>Musculoskeletal</td><td>Muscle discomfort</td><td>Muscle discomfort</td><td>Muscle discomfort
Unexplained generalised muscle weakness</td><td>Myalgia
Unexplained generalised muscle weakness
Migratory arthralgia without joint swelling or redness</td></tr>
<tr><td>Immune</td><td></td><td></td><td></td><td>Swollen or painful lymph nodes</td></tr>
<tr><td>Supportive criteria[1] (SBV)</td><td>At least three (3)</td><td>At least four (4)</td><td>At least five (5)</td><td>At least five (5)</td></tr>
<tr><td>Exertion intolerance</td><td colspan="4">Post-exertional malaise lasting more than 24 hours
Prolonged generalised fatigue from levels of exercise that would have been easily tolerated in the patient’s premorbid state</td></tr>
<tr><td rowspan="2">Immune</td><td>Swollen or painful lymph nodes</td><td>Swollen or painful lymph nodes</td><td>Swollen or painful lymph nodes</td><td></td></tr>
<tr><td colspan="4">Mild fever or chills or Sore throat
Infection at onset or presentation corroborated by laboratory evidence</td></tr>
<tr><td rowspan="2">Musculoskeletal</td><td colspan="4">Muscle pain, multijoint pain without swelling or redness</td></tr>
<tr><td>Unexplained generalised muscle weakness</td><td>Unexplained generalised muscle weakness</td><td></td><td></td></tr>
<tr><td rowspan="2">Reduced functional or mental capacity</td><td></td><td></td><td></td><td>Severe debilitating fatigue affecting physical and mental functioning</td></tr>
<tr><td colspan="4">Substantial functional impairment</td></tr>
<tr><td>Neurological and cognitive</td><td colspan="4">Generalised headaches (of type, severity, or pattern different from headaches the patient may have had in the premorbid state)
Cognitive symptoms (difficulty thinking, substantial impairment in short-term memory and forgetfulness)
Migraine</td></tr>
<tr><td>Other variables with individual discriminant ability</td><td colspan="3"></td><td>Orthostatic intolerance or other autonomic manifestation
Loss of thermostatic ability or other neuroendocrine manifestation</td></tr>
<tr><td rowspan="2">Exclusions[2]</td><td>Anxiety disorder</td><td>Anxiety disorder
Depression</td><td>Anxiety disorder
Depression</td><td>Anxiety disorder
Depression
Hypothyroidism
Fibromyalgia</td></tr>
<tr><td colspan="4">Includes existing alternate illnesses medically proven to explain the CFS/ME symptoms (DA)</td></tr>
</table>

[1] Abbreviated as Supp.
[2] Abbreviated as Exc.

5.7.1. Summary of the classification rule for Model A (*see Table 52 for specific criteria*)

The requirements for CFS/ME case identification in the absence of alternate illnesses medically proven to explain the CFS/ME symptoms are:

(i) The presence of all three (3) mandatory criteria items considered as predictive of CFS/ME and the exclusion of the cases in which anxiety disorder is present (Sensitivity=94.5%, specificity=57.1% corresponding to 85.4% of correctly classified cases) and;

(ii) The presence of any three supportive criteria items considered as highly prevalent and associated with CFS/ME.

Other criteria that may be associated with CFS/ME but are least required for CFS/ME case-identification include migraine, unexplained generalised muscle weakness and substantial functional impairment.

From a public health perspective, the sensitivity of a case-definition is usually considered to be more important than specificity (i.e. false-positives are more acceptable than false negatives). Therefore this approach may be particularly useful for public health purposes and would represent a highly sensitive epidemiological case-definition as it assigned the majority (approximately 95%) of CFS/ME cases to the correct group.

However, a situation where this approach may not be considered i.e. whereby the elimination of false-negative cases is not preferable to that of false-positive cases, would be in a clinical study where the primary objective was to develop a tool that would reliably identify the CFS/ME population for different and specific purposes such as collecting specimens to identify markers of disease activity or identifying participants for enrolment in clinical trials.

Table 53 compares the classification rules for Model A against other case-definitions. The individual features of each case-definition that were fulfilled are presented.

For the mandatory criteria:

- Model A shared a feature (a reduction in activity to less than 50% of the patient's premorbid activity) with the Holmes and Canadian definitions and another feature (severe debilitating fatigue affecting physical and mental functioning) with the Oxford and Canadian definitions.
- The only feature not listed in the other definitions as mandatory criteria but that was present in Model A was muscle discomfort.

Table 53 Model A case classification criteria compared against CFS/ME clinical research and ME criteria (core requirements)

	Model A	Holmes	Fukuda	Oxford	PIFS	Australian	Canadian
Mandatory criteria							
A reduction in activity to less than 50% of the patient's premorbid activity	X	X					X
Severe debilitating fatigue affecting physical and mental functioning	X			X			X
Muscle discomfort	X						
Debilitating (severe) fatigue not relieved by bed rest		X	X				
New onset		X	X				X
Substantial functional impairment			X				X
Infection at onset or presentation corroborated by laboratory evidence					X		
Mental fatigue				X			X
Significant disruption of usual daily activities						X	
Chronic persisting or relapsing fatigue						X	X
Neuropsychiatric dysfunction including impairment of concentration, new onset of short term memory impairment						X	Supp.

Only features used in the classification rule to describe each model are selected. Not selecting a feature does not necessarily mean that a case classified under that model does not have the symptom.

Table 54 highlights the similar features between Model A and other case-definitions. These include:

- One supportive feature (unexplained generalised muscle weakness) and an exclusion (anxiety disorder) with the Holmes definition
- Two supportive features with the Fukuda definition (post-exertional malaise lasting more than 24 hours, muscle pain, multijoint pain without swelling or

redness)

- Two supportive features with the Canadian definition (post-exertional malaise lasting more than 24 hours and muscle weakness).

Table 54 Model A case classification criteria compared against CFS/ME clinical research criteria (supportive and exclusionary requirements)

	Model A	**Holmes**	**Fukuda**	**Oxford**	**PIFS**	**Australian**	**Canadian**
Supportive criteria							
Post-exertional malaise lasting more than 24 hours	X		X			X	core
Muscle discomfort or myalgia		X	X	X			X
Migratory arthralgia without joint swelling or redness		X	X				X
Muscle pain, multijoint pain without swelling or redness	X		X				
Prolonged generalised fatigue from levels of exercise that would have been easily tolerated in the patients premorbid state		X					
Unexplained generalized muscle weakness	X	X					X
Swollen lymph nodes	X	X					
Painful lymph nodes			X				X
Sore throat		X	X				X
Mild fever or chills		X					
Sleep disturbance		X	X	X			core
Generalized headaches of a new type, severity, or pattern		X	X				X
Neurocognitive or psychological symptoms		1 or more				core	core ≥2
▪ Forgetfulness		X					
▪ Confusion		X					X
▪ Difficulty thinking		X					X
▪ Inability to concentrate		X	X				X
▪ Excessive irritability		X					
▪ Substantial impairment in short-term memory			X				X
▪ Photophobia		X					X
▪ Transient visual scotomata,		X					
▪ Depression		X					X
Perceptual and sensory disturbances							X
Ataxia							X
Muscle weakness and fasciculations							X
Hypersensitivity to noise and/or emotional overload							X
Autonomic, neuroendocrine and/or immune manifestations							core ≥1
Description of the main symptom complex as initially developing over a few hours to a few days		X					
Exclusions in addition to existing alternate illnesses medically proven to explain the CFS/ME symptoms	X	X	X	X		X	X.
▪ Anxiety disorder	X	X					
▪ Depression							
▪ Hypothyroidism							X
▪ Fibromyalgia							

5.7.2. Summary of the classification rule for Model B

The classification rule for CFS/ME in the absence of an existing alternate illness that has been medically proven to explain the CFS/ME symptoms requires:

(i) The presence of all three (3) mandatory criteria items considered as predictive of CFS/ME with the exclusion of the cases in which anxiety disorder and depression are present (sensitivity= 91.8%, specificity= 66.0% corresponding to 83.3% of correctly classified cases) and;

(ii) The presence of any four (4) supportive criteria items considered as highly prevalent and associated with CFS/ME.

The mandatory and supportive criteria for this model were identical to those in Model A with the exception that some additional features were required for the supportive criteria compromised of flu-like symptoms. Amongst the four models, Model B was the only one to include the majority of flu-like symptoms thus suggesting a possible infectious association.

Another difference was the inclusion of depression alongside anxiety disorder as exclusionary criteria which probably explained why the model might be less sensitive compared to Model A. Other criteria that could be associated with CFS/ME in this model which were less required for CFS/ME case-identification included painful lymph nodes, unexplained generalised muscle weakness, and substantial functional impairment.

The individual features of each case-definition that were fulfilled are presented in Table 55. This shows a pattern similar to Model A, in relation to the features common to both Model B and other case-definitions. These were:

- One feature (a reduction in activity to less than 50% of the patient's premorbid activity) with the Holmes and Canadian definitions
- One feature (severe debilitating fatigue affecting physical and mental functioning) with the Oxford and Canadian definitions.

Likewise, the only feature not listed in the other definitions as mandatory criteria but was present in Model B was muscle discomfort.

Table 55 Model B Case classification criteria compared against CFS/ME clinical research criteria (core requirements)

	Model B	Holmes	Fukuda	Oxford	PIFS	Australian	Canadian
Mandatory criteria							
A reduction in activity to less than 50% of the patient's premorbid activity	X	X					X
Severe debilitating fatigue affecting physical and mental functioning	X			X			X
Muscle discomfort	X						
Debilitating (severe) fatigue not relieved by bed rest		X	X				
New onset		X	X				X
Substantial functional impairment			X				
Infection at onset or presentation corroborated by laboratory evidence					X		
Mental fatigue				X			X
Significant disruption of usual daily activities						X	
Chronic persisting or relapsing fatigue						X	X
Neuropsychiatric dysfunction including impairment of concentration, new onset of short term memory impairment						X	

Table 56 shows the supportive features common to Model B and other definitions. These were:

- Three (3) supportive features (sore throat, painful lymph nodes, swollen lymph nodes) and an exclusion (anxiety disorder) with the Holmes definition
- Two (2) supportive features with the Fukuda definition (post-exertional malaise lasting more than 24 hours, muscle pain, multijoint pain without swelling or redness)
- Two (2) supportive features with the Australian definition (post-exertional malaise lasting more than 24 hours, neuropsychological symptoms)
- Three (3) supportive features with the Canadian definition (post-exertional malaise lasting more than 24 hours, sore throat and painful lymph nodes).

Table 56 Model B case classification criteria compared against CFS/ME clinical research criteria (supportive and exclusionary requirements)

	Model B	**Holmes**	**Fukuda**	**Oxford**	**PIFS**	**Australian**	**Canadian**
Supportive criteria	At least four (4)	At least eight (8) of eleven (11)	At least four (4)				At least two (2)
Post-exertional malaise lasting more than 24 hours	X		X			X	core
Muscle discomfort or myalgia		X	X	X			X
Migratory arthralgia without joint swelling or redness		X	X				X
Muscle pain, multijoint pain without swelling or redness	X						
Prolonged generalised fatigue from levels of exercise that would have been easily tolerated in the patients premorbid state		X					
Unexplained generalized muscle weakness.		X					X
Swollen lymph nodes	X	X					
Painful lymph nodes	X		X				X
Sore throat	X	X	X				X
Mild fever or chills	X	X					
Sleep disturbance		X	X	X			core
Generalized headaches of a new type, severity, or pattern		X	X				X
Neurocognitive or psychological symptoms		1 or more				X	core ≥2
▪ Forgetfulness		X					
▪ Confusion		X					X
▪ Difficulty thinking		X					X
▪ Inability to concentrate		X	X				X
▪ Excessive irritability		X					
▪ Substantial impairment in short-term memory			X				X
▪ Photophobia		X					X
▪ Transient visual scotomata,		X					
▪ Depression		X					
Perceptual and sensory disturbances							X
Ataxia							X
Muscle weakness and fasciculations							X
Hypersensitivity to noise and/or emotional overload							X
Autonomic, neuroendocrine and/or immune manifestations							core ≥1
Description of the main symptom complex as initially developing over a few hours to a few days		X					
Exclusions in addition to existing alternate illnesses medically proven to explain the CFS/ME symptoms		X	X	X		X	X.
▪ Anxiety disorder	X	X					
▪ Depression	X						
▪ Hypothyroidism							X
▪ Fibromyalgia							

5.7.3. Summary of the classification rule for Model C

The requirements for CFS/ME case identification in the absence of alternate illnesses which have been medically proven to explain the CFS/ME symptoms are:

(i) The presence of all four mandatory criteria items considered as predictive of CFS/ME with the exclusion of the cases in which anxiety disorder and depression are present (sensitivity=82.7%, specificity=69.8% corresponding to 77.1% of correctly classified cases) and;

(ii) The presence of any five supportive criteria items considered as highly prevalent and associated with CFS/ME.

The mandatory and supportive criteria for this model are similar to those in Model B with the exception that an additional criterion is required both for the mandatory (unexplained generalised muscle weakness or generalised headaches of type, severity, or pattern different from headaches the patient may have had in the premorbid state) and supportive criteria (cognitive symptoms- difficulty thinking and substantial impairment in short-term memory). These differences also seem to impact on the sensitivity of the model which is less compared to Models A and B.

Table 57 shows the mandatory features common to Model C and the other case-definitions. These were:

- A reduction in activity to less than 50% of the patient's premorbid activity (Holmes and Canadian),
- Severe debilitating fatigue affecting physical and mental functioning (Oxford and Canadian).

The exclusion of anxiety disorder was common to Model B and the Holmes definition.

Table 57 Model C Case classification criteria compared against CFS/ME clinical research criteria (core requirements)

	Model C	Holmes	Fukuda	Oxford	PIFS	Australian	Canadian
Total number of criteria required	9	10					
Mandatory criteria							
A reduction in activity to less than 50% of the patient's premorbid activity	X	X					X
Severe debilitating fatigue affecting physical and mental functioning	X			X			X
Muscle discomfort	X						
Debilitating (severe) fatigue not relieved by bed rest		X	X				
New onset		X	X				X
Substantial functional impairment			X				X
Infection at onset or presentation corroborated by laboratory evidence					X		
Mental fatigue				X			X
Significant disruption of usual daily activities						X	
Chronic persisting or relapsing fatigue						X	X
Neuropsychiatric dysfunction including impairment of concentration, new onset of short term memory impairment						X	Supp.
Unexplained generalised muscle weakness	X						

Table 58 presents features common to both Model C and the other case-definitions in relation to the supportive criteria were:

- Post-exertional malaise lasting more than 24 hours (Fukuda, Australian and Canadian definitions)
- Prolonged generalised fatigue from levels of exercise that would have been easily tolerated in the patients premorbid state (Holmes)
- Unexplained generalized muscle weakness (Holmes and Canadian definitions)
- Sore throat (Holmes, Fukuda and Canadian definitions)
- Mild fever or chills (Holmes)
- Generalised headaches of a new type, severity, or pattern (Holmes, Fukuda and Canadian definitions)
- Difficulty thinking or neuropsychological symptoms (Holmes, Australian and Canadian definitions).

Table 58 Model C case classification criteria compared against CFS/ME clinical research criteria (supportive and exclusionary requirements)

	Model C	**Holmes**	**Fukuda**	**Oxford**	**PIFS**	**Australian**	**Canadian**
Supportive criteria	At least five (5)	At least eight (8) of eleven (11)	At least four (4)				At least two (2)
Post-exertional malaise lasting more than 24 hours	X		X			X	core
Muscle discomfort or myalgia		X	X	X			X
Migratory arthralgia without joint swelling or redness		X	X				X
Muscle pain, multijoint pain without swelling or redness	X						
Prolonged generalised fatigue from levels of exercise that would have been easily tolerated in the patients premorbid state	X	X					
Unexplained generalized muscle weakness	core	X					X
Swollen lymph nodes	X	X					
Painful lymph nodes			X				X
Sore throat	X	X	X				X
Mild fever or chills	X	X					
Sleep disturbance		X	X	X			core
Generalised headaches of a new type, severity, or pattern	X	X	X				X
Neurocognitive or psychological symptoms	X	1 or more				X	core ≥2
▪ Forgetfulness		X					
▪ Confusion		X					X
▪ Difficulty thinking	X	X					X
▪ Inability to concentrate		X	X				X
▪ Excessive irritability		X					
▪ Impairment in short-term memory			X				X
▪ Photophobia		X					X
▪ Transient visual scotomata,		X					
▪ Depression		X					
Perceptual and sensory disturbances							X
Ataxia							X
Hypersensitivity to noise and/or emotional overload							X
Autonomic, neuroendocrine and/or immune manifestations							core ≥1
Description of the main symptom complex as initially developing over a few hours to a few days		X					
Exclusions in addition to existing alternate illnesses medically proven to explain the CFS/ME symptoms		X	X	X		X	X.
▪ Anxiety disorder	X	X					
▪ Depression	X						
▪ Hypothyroidism							X
▪ Fibromyalgia syndrome							

5.7.4. Summary of the classification rule for Model D

The requirements for CFS/ME case identification in the absence of alternate illnesses which have been medically proven to explain the CFS/ME symptoms were:

(i) The presence of all five mandatory criteria items considered as predictive of CFS/ME with the exclusion of the cases in which anxiety disorder, depression, hypothyroidism and fibromyalgia are present (sensitivity=76.9, specificity=88.0% corresponding to 84.0% of correctly classified cases) and;

(ii) The presence of any five supportive criteria items considered as highly prevalent and associated with CFS/ME.

The mandatory criteria for this model differed slightly from the other models. Compared with Model C, swollen lymph nodes and migratory arthralgia without joint swelling or pain were required for the mandatory criteria whilst severe debilitating fatigue affecting physical and mental functioning and unexplained generalised muscle weakness or generalised headaches (of type, severity, or pattern different from headaches the patient may have had in the premorbid state) are excluded from the mandatory requirement.

The additional supportive criteria included for Model D which were not a part of the SBV analysis included orthostatic intolerance or other autonomic manifestation and loss of thermostatic ability or other neuroendocrine manifestation. These two variables were added because they demonstrated individual discriminative ability. The exclusionary criteria also included fibromyalgia and hypothyroidism. These were two additional features which were not present in the other models.

Model D had the highest threshold and number of features required for a case to be included in comparison to the other models and thus produced a stricter classification rule. There was an increase in the number of features within the supportive criteria (12 in total) which was deemed suggestive of a different pattern of symptomatology or an increased severity of illness. As a result, this model was also presented as a case-definition for CFS/ME although, a highly specific epidemiological

case-definition that would reliably identify the severe cases of CFS/ME present in the population for surveillance and reporting purposes.

The mandatory criteria required for the classification rule for Model D, which were also present in other case-definitions, are reported in Table 59. These were:

- A reduction in activity to less than 50% of the patient's premorbid activity (Holmes and the Canadian definitions)
- Myalgia (Canadian definition).

Table 59 Model D Case classification criteria compared against CFS/ME clinical research criteria (core requirements)

	Model D	Holmes	Fukuda	Oxford	PIFS	Australian	Canadian
Total number of criteria required	10	10					
Mandatory criteria							
A reduction in activity to less than 50% of the patient's premorbid activity	X	X					X
Severe debilitating fatigue affecting physical and mental functioning	Supp.			X			X
Myalgia	X						X
Debilitating (severe) fatigue not relieved by bed rest		X	X				
New onset		X	X				X
Substantial functional impairment			X				X
Infection at onset or presentation corroborated by laboratory evidence	Supp.				X		
Mental fatigue				X			X
Significant disruption of usual daily activities						X	
Chronic persisting or relapsing fatigue						X	X
Neuropsychiatric dysfunction including impairment of concentration, new onset of short term memory impairment	Supp.	Supp.	Supp.			X	Supp.
Unexplained generalised muscle weakness	X						
Swollen lymph nodes	X						
Migratory arthralgia without joint swelling or redness	X						

Table 60 presents the features required in the supportive criteria for Model D which were also common to other case-definitions. There were 10 features common to the Holmes and Canadian definition, eight features common to Fukuda, two features common to the Oxford and another two features common to the Australian definition. Thus amongst the four models, Model D appeared to share more features with the clinical research definitions.

Table 60 Model D case classification criteria compared against CFS/ME clinical research criteria (supportive and exclusionary requirements)

	Model D	**Holmes**	**Fukuda**	**Oxford**	**PIFS**	**Australian**	**Canadian**
Supportive criteria	At least five (5)	At least eight (8) of eleven (11)	At least four (4)				At least two (2)
Post-exertional malaise lasting more than 24 hours	X		X			X	core
Muscle discomfort or myalgia	core	X	X	X			X
Migratory arthralgia without joint swelling or redness	core	X	X				X
Muscle pain, multijoint pain without swelling or redness	X						
Prolonged generalised fatigue from levels of exercise that would have been easily tolerated in the patients premorbid state	X	X					
Muscle weakness	core	X					X
Swollen lymph nodes	core	X					
Painful lymph nodes	X		X				X
Sore throat	X	X	X				X
Mild fever or chills		X					
Infection at onset or presentation corroborated by laboratory evidence	X				core		
Sleep disturbance		X	X	X			core
Generalized headaches of a new type, severity, or pattern	X	X	X				X
Neurocognitive or psychological symptoms	X	1 or more	X			core	core ≥2
▪ Forgetfulness	X	x					
▪ Confusion		x					X
▪ Difficulty thinking	x	x					X
▪ Inability to concentrate		x	X				X
▪ Excessive irritability		x					
▪ Substantial impairment in short-term memory	X		X				X
▪ Photophobia		x					X
▪ Transient visual scotomata,		x					
▪ Depression	Exc.	x					
Perceptual and sensory disturbances							X
Ataxia							X
Hypersensitivity to noise and/or emotional overload							X
Autonomic, neuroendocrine and/or immune manifestations	X						core ≥1
Description of the main symptom complex as initially developing over a few hours to a few days		X					
Exclusions in addition to existing alternate illnesses medically proven to explain the CFS/ME symptoms	X	X	X	X		X	X
▪ Anxiety disorder	X	X					
▪ Depression	X						
▪ Hypothyroidism	X						X
▪ Fibromyalgia	X						

5.7.5. Summary of the development of the case-definition algorithm

A two-level case-definition for CFS/ME is proposed. The summary of the development and testing of the case-definition algorithm for CFS/ME is shown in the flowcharts below.

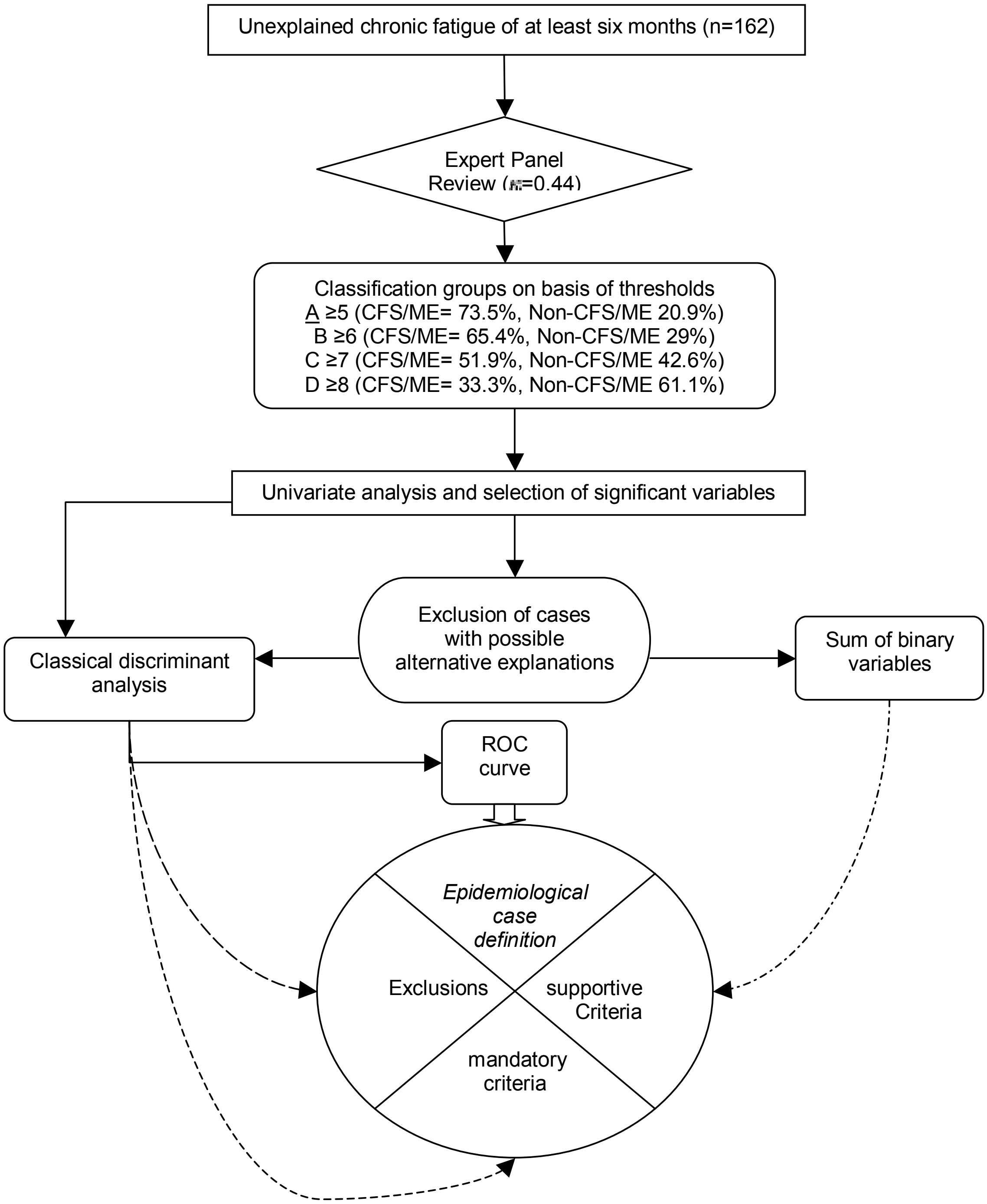


Figure 21 Flow chart of the development and testing of case-definition algorithm

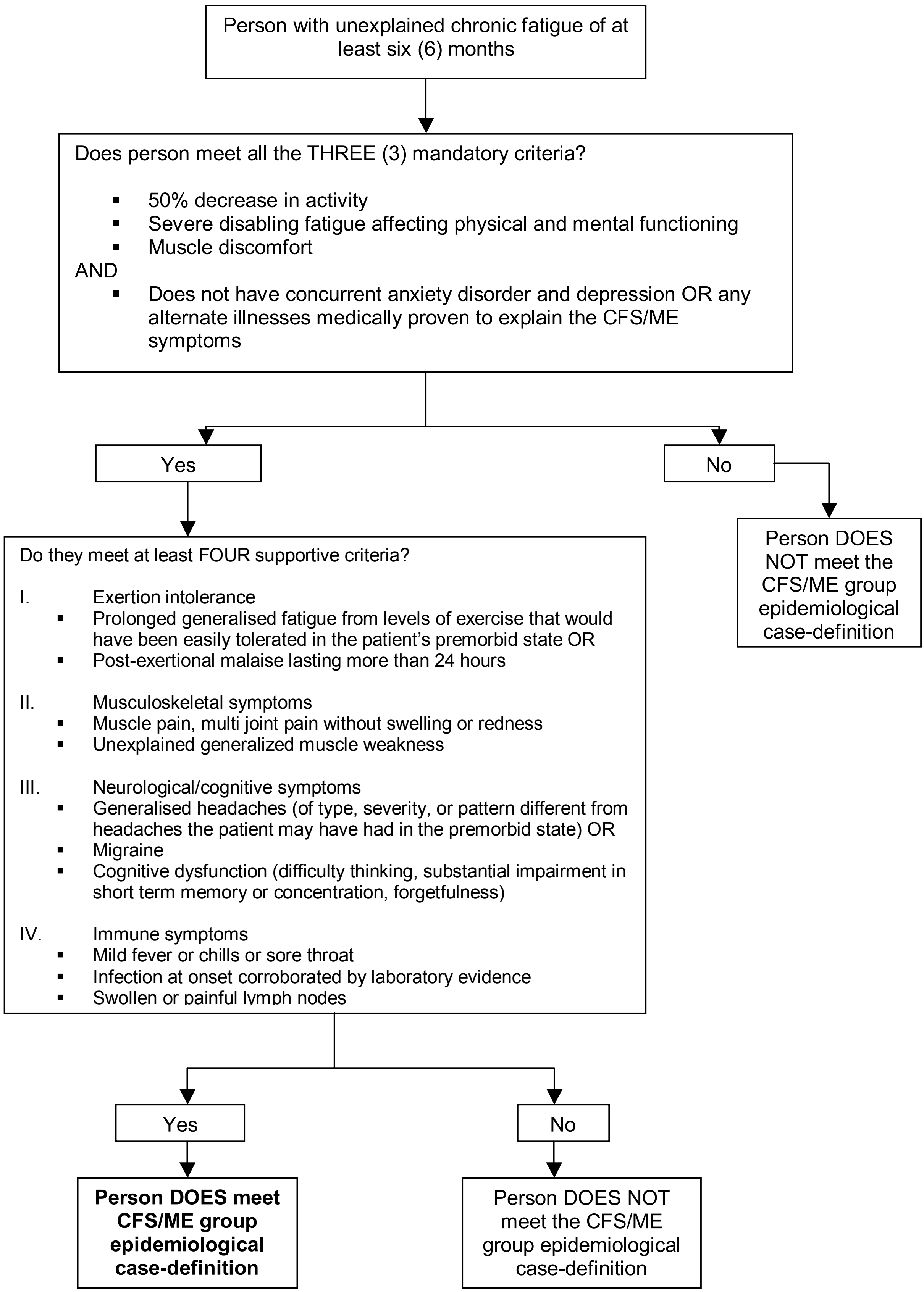


Figure 22 Flowchart of the sensitive CFS/ME epidemiological case-definition algorithm

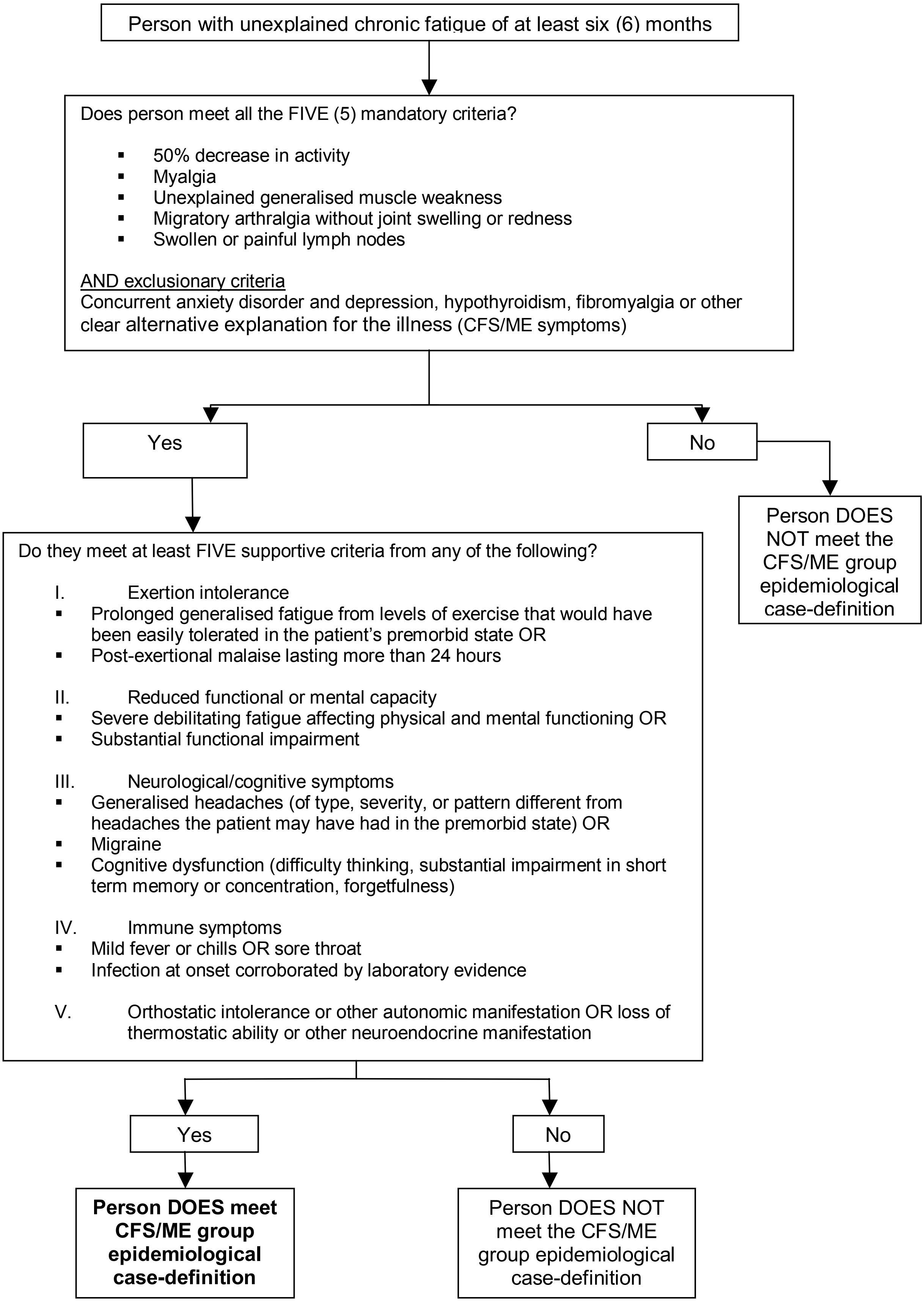


Figure 23 Flowchart of the specific CFS/ME epidemiological case-definition algorithm

Accurate detection of CFS/ME cases is important for reporting. In this study, a case was defined mostly through self-reported symptoms. By applying exploratory statistical methods for the CFS/ME case-definition, it was possible to develop a sensitive tool that maintained the balance between accuracy and field practicality. Classification criteria with a higher specificity were also postulated which could be extended to situations requiring surveillance of patients with more severe symptoms or in the comparison of studies assessing similar subgroups of patients.

5.8. Sensitivity analyses comparing classifications

5.8.1. Sensitivity-analyses to test the impact of the clinical research definitions on the gold standard

The proportion of cases identified by the gold standard review that were either CFS/ME or non-CFS/ME, which matched with cases identified with the clinical research definitions was computed. Sensitivity analyses were then performed at the different thresholds levels to examine the effect of varying the thresholds on case-selection by the clinical research definitions used in the study when they were applied to the gold standard. This was to assess the sensitivity of the estimates of accuracy of each dataset to changes in the rates of true positives and true negatives. The published CFS/ME clinical research criteria that were compared relative to the gold standard were the Holmes (CDC 1988), Fukuda (CDC 1994), Australian and the Oxford case-definitions.

The results of previous validation procedures from the discriminant analysis were used to determine the sensitivity and specificity levels above or below which the set of clinical criteria performed optimally or remained unchanged as well as their accuracy.

Case allocation was undertaken by generating algorithms from case-identification criteria in the clinical research definitions (see Appendix F) using the SPSS 'select cases' facility which were then applied to all 162 records. The cases classified by each clinical research definition were then cross tabulated against the reviewers' judgement at the different threshold levels. At first, the assessment included all cases in the study, thus no cases were excluded on basis of exclusionary conditions. However, when each clinical research case-definition was applied, cases with any exclusionary criteria included in the particular clinical research case-definition were assessed as non-CFS/ME.

As exclusionary criteria vary from definition to definition, a second assessment was made whereby all exclusionary conditions from each case-definition were compiled and cases with either of these conditions excluded from the analysis. This was done to examine the impact of the exclusionary criteria on the analysis. The charts produced in this section were developed using Microsoft Excel 2000.

A full table of the results is included in Appendix P. The results summary for each case-definition is presented as follows:

5.8.2. Sensitivity-analyses to test the impact of the Holmes definition on the gold standard

The proportion of the gold standard review CFS/ME cases identified by the Holmes definition at the four levels I, II, III and IV were 7.8%, 7.8%, 7.2% and 6.5% respectively. This represented a decrease in the proportion of cases identified using the Holmes definition from the lowest to the highest threshold of the gold standard. The highest agreement between the Holmes definition and the gold standard occurred at level IV (70%) whilst the lowest agreement occurred at level I (30%).

Table 61 is a summary of the comparison of the performance of the Holmes definition compared against the gold standard review.

Table 61 Sensitivity analyses of the Holmes definition against the gold standard review

	Comparison to the gold standard review			
Holmes case-definition	**Level I (A)**	**Level II (B)**	**Level III (C)**	**Level IV (D)**
Cases with exclusionary criteria included				
Sensitivity I	10.1	11.3	13.1	18.5
Specificity I	100.0	100.0	98.6	98.0
PPV I	100.0	100.0	91.7	83.3
Cases with exclusionary criteria excluded				
Sensitivity II	7.7	9.4	12.0	16.7
Specificity II	100.0	100.0	100.0	97.9
PPV II	100.0	100.0	100.0	66.7
Overall agreement (%)	*30.2*	*38.5*	*51.6*	*69.9*

The results shown in Table 61 indicate that:

I. Generally, application of the Holmes definition resulted in poor sensitivity at 10.1%, 11.3%, 13.1% and 18.5% across the four thresholds of the gold standard I, II, III and IV respectively. This suggested an incomplete identification of gold standard CFS/ME cases within the study population. In contrast, the Holmes definition was highly specific for the gold standard non-CFS/ME cases.

II. The positive predictive value measured how likely it was that a case really had CFS/ME, given that the Holmes definition results were positive. Thus proportion of those who were classified as CFS/ME when the Holmes definition was applied, who had CFS/ME according to the gold standard (positive predictive value) were 100%, 100%, 91.7% and 83.3% across the four levels I, II, III and IV respectively. Thus in every 100 cases with a positive outcome, all persons classified at levels I and II, 92 persons classified at level III and 83 persons at level IV of the 100 will have CFS/ME.

III. The Holmes definition was sensitive to the application of exclusionary criteria to the gold standard. Generally the sensitivity decreased when the exclusionary criteria were applied to the gold standard and cases with a possible alternative explanation for the illness were excluded from the analysis. In contrast, the specificity and positive predictive values increased except at the last level (IV).

The impact of the Holmes definition when applied to the gold standard is depicted in the chart in Figure 24 in terms of performance of the classification system.

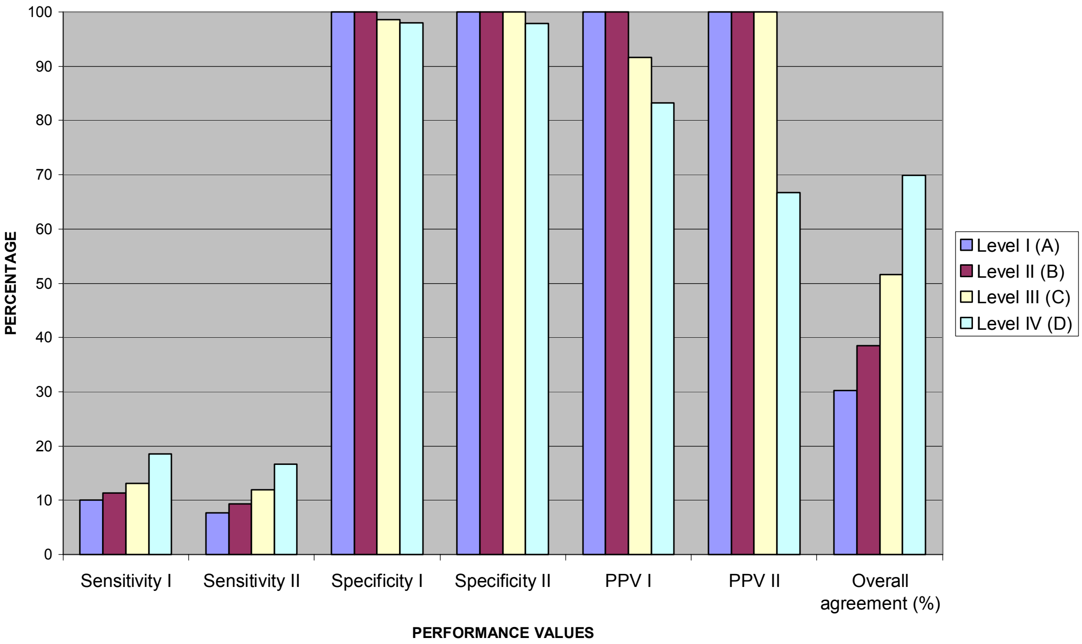


Figure 24 Performance of the Holmes case-definition in relation to the gold standard

Key	Descriptions
Sensitivity I	The proportion of true positives of all positive cases in the study population when exclusionary criteria were not applied i.e. including cases with a possible alternative diagnosis
Sensitivity II	The proportion of true positives of all positive cases in the study population when exclusionary criteria were applied i.e. excluding cases with a possible alternative diagnosis
Specificity I	The proportion of true negatives of all negative cases in the study population when the exclusionary criteria were not applied
Specificity II	The proportion of true negatives of all negative cases in the study population when the exclusionary criteria were applied
PPV I	The proportion of cases with positive outcome from the gold standard that are correctly classified by the clinical research definition when the exclusionary criteria were not applied
PPV II	The proportion of cases with positive outcome from the gold standard that are correctly classified by the clinical research definition when the exclusionary criteria were applied
Overall agreement (%)	Proportion of CFS/ME and non-CFS/ME cases within the total study population agreed by both the gold standard and the clinical research definition i.e. the overlap in case-classification.

5.8.3. Sensitivity-analyses to test the impact of the Fukuda definition on the gold standard review

The proportion of the gold standard CFS/ME cases correctly matched at the four threshold levels I, II, III and IV were 34.4%, 32.7%, 29.4% and 22.2% respectively when the Fukuda case-definition was applied. Similar to the Holmes definition, this represented a decrease in the proportion of cases from the lowest to the highest threshold. The highest agreement between the Fukuda definition and the gold standard occurred also at level IV (73.2%) whilst the lowest agreement occurred at level I (56.2%). However the Fukuda definition improved over the Holmes definition in this respect.

Table 62 is a summary of the results of the impact of the Fukuda definition on the gold standard.

Table 62 Sensitivity analyses of the Fukuda definition against the gold standard review

	Comparison to the gold standard review			
Fukuda case-definition	**Level I (A)**	**Level II (B)**	**Level III (C)**	**Level IV (D)**
Cases with exclusionary criteria included				
Sensitivity I	44.5	47.2	53.6	63.0
Specificity I	94.3	89.4	85.5	78.8
PPV I	96.4	90.9	81.8	61.8
Cases with exclusionary criteria excluded				
Sensitivity II	30.8	34.4	40.0	41.7
Specificity II	100.0	96.3	94.1	85.1
PPV II	100.0	91.7	83.3	41.7
Overall agreement (%)	*56.2*	*60.1*	*68.0*	*73.2*

The results shown in Table 62 suggest that

I. Application of the Fukuda definition resulted in low sensitivity relative to the gold standard, though it was much higher than when the Holmes definition was applied at 44.5%, 47.2%, 53.6% and 63% across levels I, II, III and IV respectively. However

specificity was good relative to the gold standard but lower than with the Holmes definition at 94.3%, 89.4%, 85.5% and 78.8% across levels I, II, III and IV respectively.

II. Though the positive predictive values were good (96.4%, 90.9%, 81.8% and 61.8% at levels I, II, III and IV respectively) at higher thresholds of the gold standard, it was less likely that cases with a positive outcome from the gold standard would be correctly identified by using the Fukuda definition.

III. The Fukuda definition was also sensitive to the application of exclusionary criteria to the gold standard. The sensitivity decreased when the exclusionary criteria were applied to the gold standard and cases with a possible alternative explanation for the illness were excluded from the analysis, whereas the specificity and positive predictive values increased.

The performance of the Fukuda definition relative to the gold standard is depicted in the chart in Figure 25.

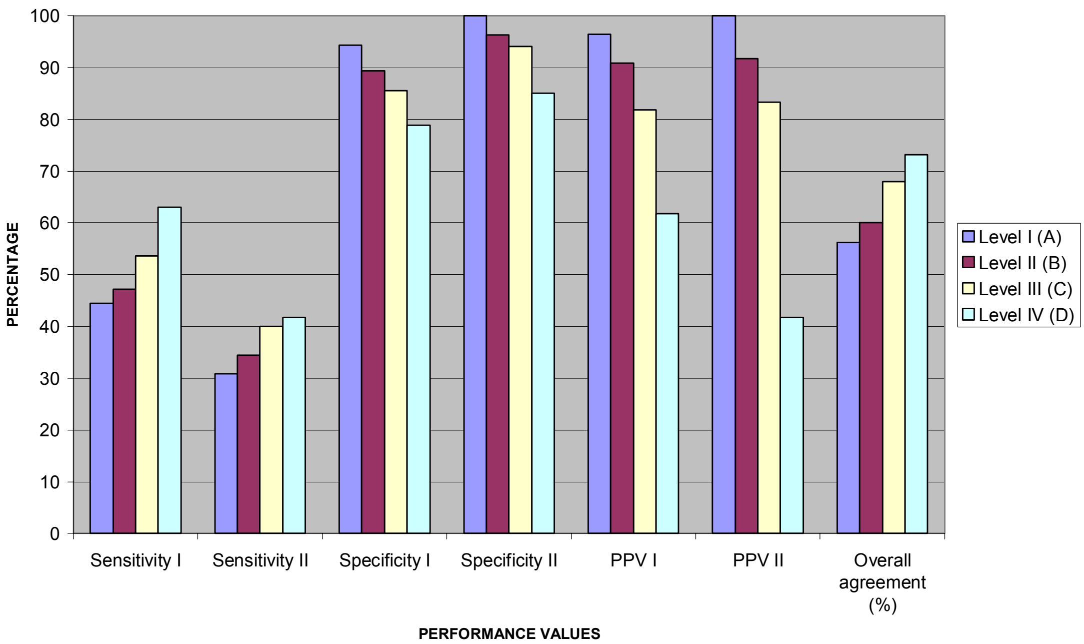


Figure 25 Performance of the Fukuda case-definition in relation to the gold standard

5.8.4. Sensitivity-analyses to test the impact of the Oxford definition on the gold standard review

In contrast to the previous definitions i.e. the Holmes and Fukuda definition, the proportion of CFS/ME cases correctly matched decreased across the four threshold levels I, II, III and IV at 57.8%, 51.6%, 40.5% and 28.1% respectively. This suggests that the Holmes and Fukuda definitions apply more stringent criteria and thus were likely to be more similar to Model D and less similar to Model A, whilst the Oxford definition was likely to be more similar to Model A and less to Model D.

Table 63 is a summary of the results of the impact of the Oxford definition on the gold standard review assessed by performance measures.

Table 63 Sensitivity analyses of the Oxford definition against the gold standard review

	Comparison to the gold standard review			
Oxford case-definition	**Level I (A)**	**Level II (B)**	**Level III (C)**	**Level IV (D)**
Cases with exclusionary criteria included				
Sensitivity I	74.8	74.5	73.8	79.6
Specificity I	54.3	46.8	39.1	38.4
PPV I	84.8	76.0	59.6	41.3
Cases with exclusionary criteria excluded				
Sensitivity II	79.5	84.4	88.0	100.0
Specificity II	45.0	44.4	41.2	36.2
PPV II	73.8	64.3	52.4	28.6
Overall agreement (%)	*69.9*	*66.0*	*58.1*	*52.9*

I. The sensitivity though varied, remained moderate across the four thresholds when the Oxford criteria were applied. However, specificity was poor and decreased across the thresholds.

II. Positive predictive values also decreased across the thresholds and were 84.8% (73.8%), 76% (64.3%), 59.6% (52.4%) and 41.3% (28.6%) at levels I, II, III and IV respectively.

III. Excluding cases with possible alternative diagnoses also appeared to have a positive impact on the Oxford definition as the sensitivity improved when this occurred. However the pattern across the thresholds for the performance measures were similar compared to when the exclusionary criteria were not applied.

The performance of the Oxford definition relative to the gold standard is depicted in the chart in Figure 26.

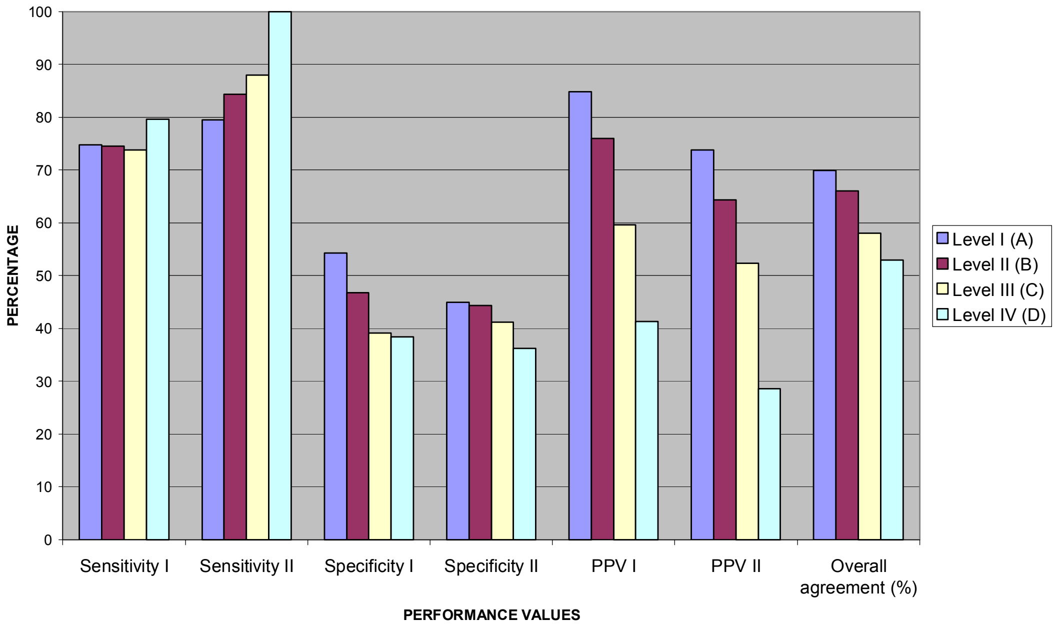


Figure 26 Performance of the Fukuda case-definition in relation to the gold standard

5.8.5. Sensitivity-analyses to test the impact of the Australian definition on the gold standard review

The proportion of CFS/ME cases correctly matched when the Australian definition was applied was low at 53.9%, 47.7%, 39.2% and 27.5% and decreased across the four threshold levels I, II, III and IV respectively.

Table 64 is a summary of the results of the impact of the Australian definition on the gold standard review assessed by performance measures.

Table 64 Sensitivity analyses of the Australian definition against the gold standard review

	Comparison to the gold standard review			
Australian case-definition	**Level I (A)**	**Level II (B)**	**Level III (C)**	**Level IV (D)**
Cases with exclusionary criteria included				
Sensitivity I	69.7	68.9	71.4	77.8
Specificity I	34.3	31.9	34.8	36.4
PPV I	78.3	69.5	57.1	40.0
Cases with exclusionary criteria excluded				
Sensitivity II	71.8	75.0	80.0	91.7
Specificity II	30.0	33.3	35.3	34.0
PPV II	66.7	57.1	47.6	26.2
Overall agreement (%)	*61.4*	*57.5*	*54.9*	*50.9*

I. Generally, the sensitivity and the specificity appeared to increase across the thresholds with an exception at level II. The specificity when the Australian definition was applied was poor and the positive predictive values also decreased at 78.3%, 69.5%, 57.1% and 40% at levels I, II, III and IV respectively.

II. The results were also sensitive to the application of exclusionary criteria. This was demonstrated by increased sensitivity on the whole and the slight decrease in specificity and positive predictive values.

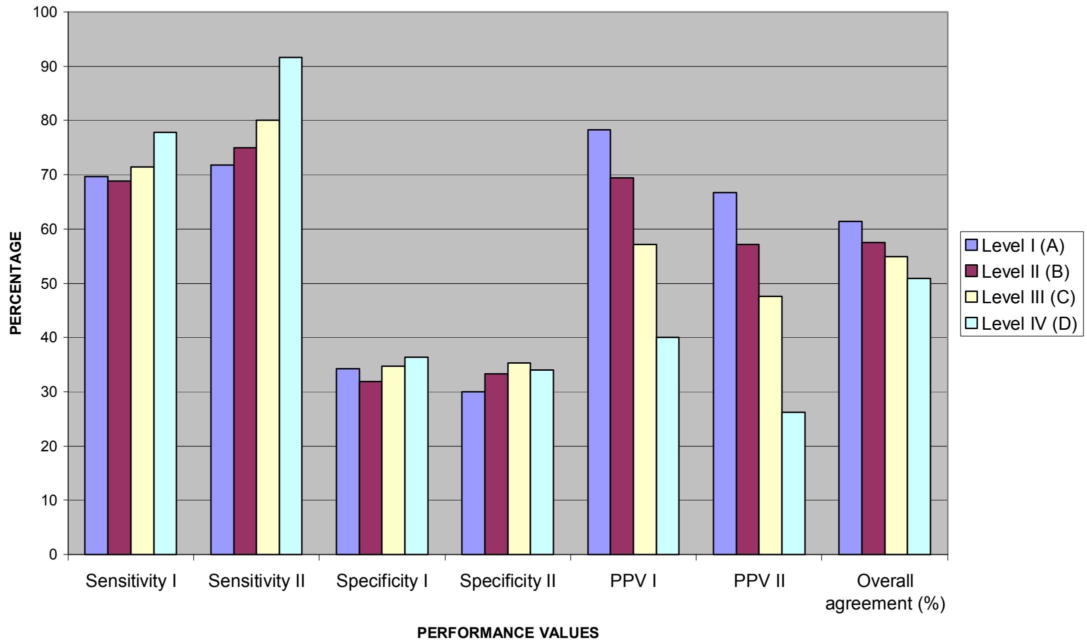


Figure 27 Performance of the Australian case-definition in relation to the gold standard

5.8.6. Summary of the sensitivity-analyses

The results suggest that the cases classified by the Australian and Oxford criteria are broadly similar and more representative of the gold standard review at level I. The rationale for the inference is that the sensitivity and accuracy increased when either criterion was used as the reference standard at the lower threshold levels I (A) and II (B). The increase in the measures may also be attributed to the requirement of fewer criteria by either case-definition to classify a case as CFS/ME as the Level I required fewer criteria for case-identification compared to Levels III and IV. At the higher thresholds III(C) and IV (D), the sensitivity improved when both the Fukuda and the Holmes criteria were applied as reference standards.

The Holmes definition had the lowest accuracy of classification of the four as its application to the gold standard resulted in low proportions of CFS/ME and non-CFS/ME cases being classified to the correct group when compared with other definitions. In terms of excluding cases with alternative medical or psychiatric illnesses,

the Oxford and Australian criteria gained in sensitivity at the expense of specificity i.e. their application to the gold standard led to more CFS/ME cases (true positives) and less non-CFS/ME cases (true-negatives) being identified. On the other hand, the Holmes and Fukuda definitions gained in specificity at the expense of sensitivity i.e. upon application of the case-definitions more people who truly did not have CFS/ME were identified however, more people who had truly had CFS/ME i.e. were true positives were left out.

In summary, the sensitivity analyses undertaken in this study have demonstrated a level of underreporting in the estimates of prevalence and accuracy of classification of CFS/ME. These measures were influenced by the different clinical research definitions (as applied in this study), their exclusionary criteria and the classification threshold or the number of criteria required for a case.

5.9. Assessment of the GPs' diagnoses

The diagnostic practices of the GPs participating in the study are reflected in Table 65.

Table 65 Frequencies of GPs diagnoses (n= 162)

Sole diagnosis of CFS/ME or ME	Frequency	Percent
CFS/ME	36	22.1
CFS	54	33.5
ME	20	12.4
Post Viral Fatigue Syndrome	4	2.5
Total	**114**	**70.5**
CFS/ME diagnosis and comorbidities		
Mixed Anxiety & Depression, CFS/ME	1	0.6
Depression, CFS/ME	1	0.6
Depression, CFS	2	1.2
Depression, CFS/ME, Fibromyalgia	1	0.6
Fibromyalgia, CFS/ME	3	1.8
Fibromyalgia Syndrome, CFS/ME	1	0.6
Total	**9**	**5.4**
CFS/ME diagnosis and other illness		
CFS/ME, Multiple Sclerosis	1	0.6
CFS/ME, Glucose Intolerance	1	0.6
CFS/ME , post Lyme disease	2	1.2
ME, Hyperglobulinaemia	1	0.6
Total	**5**	**3.0**
Non-CFS/ME diagnoses		
Bornholms disease	1	0.6
Chronic Fatigue	5	3.1
Chronic Fatigue and Depression	1	0.6
Chronic Fatigue Post Glandular Fever	1	0.6
Conversion Disorder	1	0.6
Depressive Cyclothymic Personality	1	0.6
Dysthymic Personality	1	0.6
Exhaustion Syndrome	2	1.2
Fatigue of unknown cause after full investigation	1	0.6
Fibromyalgia	1	0.6
Mood/Unhappiness	1	0.6
Myalgia	1	0.6
Polymyalgia Rheumatica	1	0.6
Post Viral Fatigue	1	0.6
Psychogenic Hyperventilation & Somatisation	1	0.6
Recurrent Depression	1	0.6
Somatisation of Anxiety	1	0.6
Total non-CFS/ME	**22**	**13.6**
No diagnosis given	12	7.5
Overall Total	**162**	**100.0**

The number of forms completed by each GP varied from a minimum of one (1) form to a maximum of four (4). 37 GPs completed one 1 form each, 18 GPs completed two (2) forms, eight (8) GPS completed three (3) forms. The remaining forms were submitted on behalf of practices and although each participating GP signed a consent form, it was not possible to determine the number of forms completed per GP in these practices as forms were submitted jointly. An average of two (2) forms was completed per GP.

The results show that CFS/ME related illness accounted for more than half of the GPs provisional diagnoses. Other diagnoses varied widely and in approximately eight percent of cases, no diagnosis was made. In approximately five percent of cases, CFS/ME was diagnosed alongside fibromyalgia and depression.

There was a clear indication that the GPs were uncertain about the diagnosis as shown in the three percent of cases where CFS/ME was diagnosed alongside other medical conditions (multiple sclerosis, glucose intolerance, Lyme disease and hyperglobulinaemia). Such conditions are clear alternative explanations for CFS/ME in some published case-definitions and would exclude a patient from the diagnosis of CFS/ME.

5.9.1. GPs diagnosis compared against the gold standard review

To assess the level of agreement between the GPs' and the reviewers, all the cases which were given a provisional diagnosis of CFS/ME or ME (including those with co morbidities and other illnesses) were assigned to the CFS/ME group, and all other diagnoses which were allocated to the non-CFS/ME group and compared with the reviewers' classification. As the reviewers were blinded to the GPs' diagnoses, it was thus possible to avoid bias during the case selection procedure.

The results of the assessment shown in Table 66 are based on the four threshold levels (cut-off scores of 5-9). Missing values (approximately 19 cases without a diagnosis) were excluded from the analyses.

Table 66 GP diagnosis versus expert reviewers' opinion of CFS/ME cases and non-CFS/ME comparison group

	Level I		Level II		Level III		Level IV		Total
	CFS/ME	*Non-CFS/ME*	*CFS/ME*	*Non-CFS/ME*	*CFS/ME*	*Non-CFS/ME*	*CFS/ME*	*Non-CFS/ME*	
CFS/ME Count	94	30	84	40	67	57	47	77	124
% within GP diagnosis (PPV CFS/ME only)	75.8	24.2	67.7	32.3	54.0	46.0	37.9	62.1	100.0
% within review (sensitivity CFS/ME only)	85.5	90.9	85.7	88.9	84.8	89.1	92.2	83.7	86.7
% of Total	65.7	21.0	58.7	28.0	46.9	39.9	32.9	53.8	86.7
Non-CFS/ME Count	16	3	14	5	12	7	4	15	19
% within GP diagnosis	84.2	15.8	73.7	26.3	63.2	36.8	21.1	78.9	100.0
% within review (specificity for non-CFS/ME only)	14.5	9.1	14.3	11.1	15.2	10.9	7.8	16.3	13.3
% of Total	11.2	2.1	9.8	3.5	8.4	4.9	2.8	10.5	13.3
Total Count	110	33	98	45	79	64	51	92	143
% within GP diagnosis	76.9	23.1	68.5	31.5	55.2	44.8	35.7	64.3	100.0
% within review	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
% of Total	76.9	23.1	68.5	31.5	55.2	44.8	35.7	64.3	100.0

The performance measures including the overall agreement between individual GPs and the reviewers at level I were as follows: sensitivity= 85.5%,

specificity= 9.1%, positive predictive value= 75.8%, negative predictive value= 15.8% and overall agreement= 67.8%. The CFS/ME diagnosis by the GPs was agreed in 65.7% of patients by the reviewers.

Hence for every 10 patients diagnosed by the GPs as having CFS/ME at level 1, approximately 8 of these will truly have the condition according to the gold standard review (PPV = 75.8%).

Of 19 patients diagnosed as non-CFS/ME by the GPs (see Table 65) at level I, only three (3) were identified as truly not having the condition i.e. true negatives. The sensitivity of GPs diagnosis of CFS/ME was 85.5% (95% confidence interval 83.5-89.3) but the specificity was extremely low at 9.1% (95% confidence interval 2.4-22.0). This was reflected in the overall agreement at 67% of cases and suggests an inclusion of greater proportion of false positive cases resulting in an over diagnosis of CFS/ME by GPs.

The level of agreement decreased at higher thresholds. At level II (cut off six), there was agreement for only 58.7 % of CFS/ME and 3.5% of non-CFS/ME cases. The overall agreement for this threshold was 62.2%.

At level III (cut off seven), there was agreement for only 46.9% CFS/ME cases and only 4.9% of the non-CFS/ME comparison group were matched. The overall agreement at this threshold was thus 51.8%.

At level IV (cut off eight), there was agreement for only 32.9% of CFS/ME cases and 10.5% of the non-CFS/ME comparison group matched. The overall agreement recorded was lowest for this threshold level at 43%.

5.9.2. GPs' diagnosis compared against a clinical case-definition

The assessment of the GPs' accuracy compared to the clinical case-definition is reflected in the Table 67. The Canadian case-definition was selected for this purpose

as it was developed purely for use in the clinical diagnoses of CFS/ME whereas the clinical research definitions were designed primarily for clinical research studies and thus may not be suited to assessment of GPs diagnostic practices (Carruthers et al. 2003).

According to this matrix, the GPs made an accurate diagnosis in 59.7% of both CFS/ME and the non-CFS/ME cases (sensitivity 91.9% and specificity 20.2%). However, only 44 persons of every 100 patients diagnosed as having CFS/ME by the GPs truly had the condition.

Table 67 GPs' diagnosis versus reviewers' opinion of CFS/ME and the non-CFS/ME comparison group

	Canadian clinical definition		Total
GPs' diagnosis	CFS/ME	Non-CFS/ME	
CFS/ME Count	57.0	71.0	128.0
% within GPs	44.5	55.5	100.0
% within Canadian	91.9	79.8	84.8
% of Total	37.7	47.0	84.8
Non-CFS/ME Count	5	18	23
% within GPs	21.7	78.3	100.0
% within Canadian	8.1	20.2	15.2
% of Total	3.3	11.9	15.2
Total Count	62.0	89.0	151.0
% within GPs	41.1	58.9	100.0
% within Canadian	100.0	100.0	100.0
% of Total	41.1	58.9	100.0

Chapter 6: Discussion

This chapter discusses the implications of the findings in relation to the aims and objectives of the research. The justification for the proposed case-definition and rationale for the various inclusion and exclusion criteria are outlined. Further, key observations from the results analyses, limitations on validity within the study, generalisability of the results, possible biases in the study and recommendations for future research are also highlighted and discussed.

6.1 Implications of study findings for the development of an epidemiological case-definition

6.1.1 The proposed epidemiological case-definition

A two-level model for the epidemiological case-definition is proposed based on Models B and D. At the first level (Model B), it would enable the utilisation of a sensitive and highly inclusive case-definition. At the second level (Model D) it would allow a more specific case-definition. In this way, the proposed case-definition would provide a tool for classifying cases of CFS/ME as a whole and subtypes of the illness in population based studies.

A description of terminology used in the case-definition is presented in Appendix M of this thesis.

I. At the first level, the definition places the emphasis of CFS/ME case-identification on the combination of three (3) mandatory criteria, at least four (4) supportive symptom criteria and exclusionary conditions. The mandatory criteria are a reduction in activity to less than 50% of the patient’s premorbid activity, severe debilitating fatigue affecting

mental and physical functioning and muscle discomfort. The supportive criteria requires a minimum of four symptoms from any of the following categories:

- Exertion intolerance: prolonged generalised fatigue from levels of exercise that would have been easily tolerated in the patient's premorbid state OR post-exertional malaise lasting more than 24 hours;
- Musculoskeletal symptoms: muscle pain, multi joint pain without swelling or redness OR unexplained generalized muscle weakness;
- Neurological or cognitive symptoms: generalised headaches (of type, severity, or pattern different from headaches the patient may have had in the premorbid state) OR migraine; cognitive dysfunction (difficulty thinking, substantial impairment in short term memory or concentration, forgetfulness);
- Immune symptoms: mild fever or chills OR sore throat OR infection at onset corroborated by laboratory evidence OR swollen or painful lymph nodes.

All cases with concurrent anxiety disorder and depression or alternate illnesses that explained the symptoms of illness are excluded.

II. At the second level, the definition places the emphasis of CFS/ME case-identification on the combination of five (5) mandatory criteria which are: a reduction in activity to less than 50% of the patient's premorbid activity, myalgia, unexplained generalised muscle weakness, migratory arthralgia without joint swelling or redness and swollen or painful lymph nodes. The supportive criteria requires a minimum of five symptoms from any of the following categories:

- Exertion intolerance: prolonged generalised fatigue from levels of exercise that would have been easily tolerated in the patient's premorbid state OR post-exertional malaise lasting more than 24 hours;
- Reduced functional or mental capacity: severe debilitating fatigue affecting physical and mental functioning OR substantial functional impairment;
- Neurological/cognitive symptoms: generalised headaches (of type, severity, or pattern different from headaches the patient may have had in the premorbid

state) OR migraine; cognitive dysfunction (difficulty thinking, substantial impairment in short term memory or concentration, forgetfulness);

- Immune symptoms (mild fever or chills OR sore throat, infection at onset corroborated by laboratory evidence);
- Orthostatic intolerance (or other autonomic manifestation) OR loss of thermostatic ability (or other neuroendocrine manifestation).

In addition, cases with concurrent anxiety disorder and depression, hypothyroidism, fibromyalgia or alternate illnesses that explain the symptoms of illness are excluded.

6.1.2 Justification for the selected epidemiological case-definition

The justification for defining a case of CFS/ME as proposed in this study are based on the characteristics of a good classification system as suggested by Wegman et al (1997).

I. The major rationale for the case-definition was to assist in epidemiological studies of CFS/ME and to allow comparisons between studies. Subjective criteria (mandatory and supportive) were required to confirm the presence or absence of CFS/ME due to the lack of objective clinical or laboratory diagnostic markers of the condition. These subjective criteria are information that is usually obtained through self-report rather than through physical examination and are available from a patient's history in medical records. On this basis, the proposed case-definition is capable of identifying CFS/ME cases from routinely or easily collected data and would facilitate data collection for epidemiological studies.

II. The justification for supportive criteria is that there were symptoms that did not form part of the mandatory symptom criteria but which had a significance of association

with the CFS/ME group, demonstrated individual discriminant ability and were also reported in 75% or more of the study population (i.e. had high "sensitivity"). On the basis of these symptoms, supportive criteria were included within the case-definition model.

III. On the basis of heterogeneity or varying symptom patterns in the population studied, a two-level definition ensured the separate classification of probably more severe CFS/ME cases and also captured the whole disease spectrum and other potential subgroups.

IV. At either level, the case-definition presented a combination of symptom criteria which demonstrated individual and group discriminant validity. On the basis of possible fluctuating CFS/ME symptoms, the supportive criteria were grouped into broader symptom categories to ensure that each aspect was represented and aided the case-definition to classify accurately to the disease group.

6.1.3 Comparison of the epidemiological case-definition with clinical research definitions

In addition to the testing performed at the different levels of certainty, another form of sensitivity analysis was performed using alternative definitions to examine the impact of these different ways of defining CFS/ME in order to determine how the differences in definition affect the results and interpretation.

During this sensitivity analysis, the bias and sensitivity in the assessment of CFS/ME as classified by the gold standard review was evaluated using the four clinical research definitions. The results of the sensitivity analysis demonstrated that the application of the four clinical research definitions to the gold standard review, led to identification of only a fraction of the cases with CFS/ME (as classified by the gold standard review).

A wide range of estimates of prevalence and accuracy of CFS/ME classification (when compared to the gold standard review) was obtained which were influenced by the clinical research definition used. Approximately between 20.4% and 89.9% (see Appendix P for full table) of the proportion of CFS/ME cases (according to the gold standard review) were underreported and classified as non-cases by the clinical research definitions as applied in this study. If these results are extrapolated to past studies based on these clinical research criteria, it may be assumed that all the clinical research definitions underestimated the prevalence of CFS/ME by excluding a proportion of probable CFS/ME cases in these studies.

Generally the values of performance measures such as sensitivity, specificity, positive and negative predictive values are related to variation in disease prevalence (Brenner, Gefeller 1997). The variance observed in the performance measures in this study are consistent with findings from other studies according to the case-definition used (refer to section 2.3.1, Table 1). This demonstrates the difficulty encountered when attempting to assess the levels of CFS/ME in population groups that were classified using these case-definitions.

Though the different case-definitions purport to classify CFS/ME as a whole, an explanation for the variation in the estimates of prevalence may be due to the number of criteria required by each case-definition for a case of CFS/ME. The clinical research definition with the highest sensitivity as applied in this study was the Oxford definition which required the least number of criteria for CFS/ME classification. The Holmes definition was the most restrictive as it had the highest specificity and also required more criteria for CFS/ME classification than any other clinical research case-definition. This finding has been documented in past studies where a group of people in the community who met the Holmes (CDC 1988) case-definition were found to have a higher frequency of symptoms and greater functional disability compared to the Fukuda (CDC 1994 case-definition) (Jason et al. 2001).

The findings revealed a similar degree of underreporting within each case-definition across the different thresholds levels which may also be related to the existence of subtypes within the population. However when the percentage agreement

levels were assessed across the thresholds, an increase was observed for the Holmes and Fukuda criteria.

The highest agreement noted for both models occurred at threshold levels III(C) and IV (D). The Fukuda definition was more sensitive than the Holmes definition and among the four clinical research definitions, it was the most identical to the gold standard review at levels III (C) and IV (D) in relation to the overall accuracy of classification. This is because it recorded the highest agreement with the gold standard review at the higher thresholds.

On the contrary, agreement decreased for the Australian and Oxford definitions across the four thresholds. Both definitions recorded a higher percentage agreement with the gold standard review at lower thresholds I (A) and II (B). The Oxford definition was the more sensitive of the two, also having the highest percentage agreement of the four clinical research definitions with the gold standard review at thresholds I and II.

These findings confirm the suggestion by some researchers that each definition may be classifying cases to different homogenous groups within the CFS/ME construct. For example in studies undertaken by De Becker, McGregor and De Meirleir (2001), they showed that the Holmes criteria selected a group of more severely affected CFS/ME patients (De Becker, McGregor & De Meirleir 2001). Another possible explanation for the differences observed in the agreement may be due to the nature or number of criteria required for a case.

It was also possible to assess the extent to which the use of the different case-definitions influenced the sensitivity. The bias estimates for both CDC case-definitions (which also had a higher requirement of number of criteria to classify a case of CFS/ME) were greater than the other two as demonstrated in the very low sensitivity of the Holmes (greatest bias) and Fukuda definitions which should preclude their use for case-identification in large-scale public health surveillance and reporting.

Although, the Australian and Oxford case-definitions (which also had lower requirement of number of criteria to classify a case of CFS/ME) had lower bias as demonstrated by the moderate to high sensitivity or prevalence estimates, specificities

below 50% were reported for both clinical research definitions across the four thresholds with the exception of the Oxford case-definition at level I (54.0%) thereby reducing their reliability for CFS/ME case-identification.

When exclusionary criteria were applied there were significant changes in the sensitivity and positive predictive values. An increase in sensitivity was observed in the Australian and Oxford groups whilst a decrease was noted in the Holmes and Fukuda groups. Conversely, the positive predictive values for the Holmes and Fukuda groups increased, whilst it decreased in the Oxford and Australian groups. This has implications for the validity of past epidemiological research studies conducted which have applied the strict exclusionary criteria from some of the clinical research definitions. To effectively assess prevalence of CFS/ME and to make comparisons between different studies, a standardized case-definition is needed which is the primary objective of this study.

6.2 Overview of methods

The primary purpose of the study was to develop a case-definition which could accurately classify CFS/ME cases irrespective of the presence of other similar illnesses and could therefore be used for epidemiological purposes. The epidemiological case-definition would be based on the parameters that were most predictive of CFS/ME group membership.

Over the course of the study, several parameters derived from current clinical research case-definitions were considered. These were based on published information deemed applicable by experienced CFS/ME researchers and included clinical signs and symptoms, comorbid and exclusionary conditions thought to be useful for classifying CFS/ME cases. The demographic features of the study population were assessed for significant associations with CFS/ME status as classified by the gold standard review but none were found between demographic variables.

Univariate analysis was conducted and certain clinical features were found to be strongly associated with CFS/ME status. To identify the best combination of these features that define CFS/ME discrimination techniques were applied using the sum of unweighted binary variables (SBV) and classical discriminant analysis (DA). Both methods were found to be useful statistical methods in constructing the case-definition model.

The SBV method of discrimination considered the increases in prevalence of symptoms or the number of parameters required to classify a case and proved to be a simpler method of assessment than the classical discriminant analysis. However it was less specific and resulted in a set of criteria which did not indicate the likelihood of each criterion in classifying CFS/ME accurately. Consequently, the SBV models were less accurate than the discriminant analysis derived models which addressed this issue.

The discriminant analysis however considered the relationships between symptoms rather than the increases in prevalence of individual symptoms (or the number of criteria required to establish the case-definition). As a result, highly prevalent

variables which did not contribute to the relationships within the discriminant model but also demonstrated individual discriminant ability were excluded. Most of these excluded variables existed in the SBV model thus to ensure that these important variables were retained in the case-definition model, the results of the discriminant analysis and SBV were combined.

6.2.1 Selection of the epidemiological case-definition model

A two-level case-definition model was proposed for several reasons which were related to:

I. The purpose for which the case-definition was required and its applicability to various situations. The classification criteria for CFS/ME were required to be of high sensitivity. This would serve a number of useful purposes in epidemiological studies such as ensuring that true CFS/ME cases can be prospectively identified in case-control or cross-sectional studies but more importantly during monitoring and surveillance activities. More stringent criteria for identifying severe cases were also postulated which would facilitate case-identification and assessment of more severe cases of CFS/ME. The higher specificity of the stringent criteria would limit the number of cases with mild to moderate CFS/ME illness or comorbid conditions or non-CFS/ME cases that may be chosen.

II. The outcome of the discriminant analysis and the sum of binary variables procedures (described in the preceding section). The study identified the significant predictors of CFS/ME (mandatory criteria) two of which were consistent for the two-level model. These were a reduction in activity to less than 50% of the patient's premorbid activity and muscle discomfort or myalgia.

III. The estimated area under the curve (AUC) of the ROC curve, (a resulting plot of probabilities that the model would correctly distinguish between two cases) from the

discriminant analysis. This provided a measure of overall accuracy based on post-test probabilities of the four models initially considered. It addressed issues resulting from the individual threshold-dependent accuracy measures (generated from the discriminant analysis), by producing results that were independent of the prevalence of the CFS/ME or non-CFS/ME groups (as classified by the gold standard review). This made it more appropriate for determining the best model as well as assessing variations in performance of all the models involved in this study.

Consideration of the initial four models (A, B, C and D)

Generally, the study results showed that various criteria differentiated between the main CFS/ME and non-CFS/ME groups. Three features of the CFS/ME group identified as predictors, remained consistent for the four models initially derived (a reduction in activity to less than 50% of the patient's premorbid activity; severe, debilitating fatigue affecting physical and mental functioning and muscle discomfort or myalgia), demonstrating the robustness of the results.

In addition, two sub-groups were identified on the basis of symptomatology. The first of these comprised Models A, B and C and they had nearly identical profiles for the mandatory and supportive criteria and lower number of reported symptoms (SBV produced 6-9 symptoms). The three features that assigned majority of the cases accurately were a reduction in activity to less than 50% of the patient's premorbid activity, severe debilitating fatigue affecting physical and mental functioning, and muscle discomfort.

On the other hand, the second group identified, comprised Model D. Since Model D had the highest threshold for CFS/ME and required a greater number of symptoms to classify a CFS/ME case (minimum of 10 symptoms), it might be concluded that the CFS/ME cases in this group are the most unequivocally ill, and possibly the more severe cases. As the results indicated that the likelihood of CFS/ME increases with increasing number of symptoms, this suggests that the condition lies on a continuum of

severity. Thus the higher the number of symptoms the more likely the result will represent a true positive outcome.

The differences between Model D and the other three models might be attributed to baseline characteristics or heterogeneity present within CFS/ME population as shown in previous studies (Bombardier, Buchwald 1995, Jason et al. 2000). Some people however, argue that the more severe cases are a different illness from the less severe cases and that severity of CFS/ME can be demonstrated by increased symptoms in patients (Jason et. al 2003). These results seem to bear that out, and, while they tell nothing about underlying pathology, they suggest a different pattern of symptomatology in the two groups and this has implications for aetiology, clinical diagnosis and management of patients.

Model D, though it could be considered a reliable set of criteria for the classification of a more clinically severe subgroup within the broader CFS/ME definition, would not capture cases with the milder form of CFS/ME thus resulting in the exclusion of cases with mild to moderate symptoms. With the exception of ‘a reduction in activity to less than 50% of the patient’s premorbid activity’ and ‘muscle discomfort’ or ‘myalgia’, the profile of other case-defining symptom criteria was quite different from the first group (Table 51).

In considering the choice of model for the final definition, thresholds were taken in account. As described in section 5.5.6, decreasing the threshold of a model, increased the number of CFS/ME cases classified, and decreased the number of non-cases. This appeared to have some impact on the performance of the models in relation to an increase in the potential for bias towards models with larger sample sizes. It also raised issues around the how many false-positive cases were acceptable if the threshold were to be lowered to accommodate the study aims which focused on developing a sensitive model at the expense of specificity.

To avoid the potential bias and error resulting from the threshold effect during assessment of model performance, an ROC curve analysis of the four models was undertaken.

The ROC curve analysis (Figure 20) formed the basis for selecting the case-definition model. Model B was thus found be best among the four models in view of its higher accuracy (demonstrated by the area under the curve), its sensitivity compared to Model C and specificity compared to Model A (refer to Table 52). Model B would be able to capture better the mixed range of mild to moderate or moderate to severe cases of CFS/ME. Model D would be more appropriate for assessing moderate to severe cases of CFS/ME.

Thus an epidemiological case-definition model is proposed at two levels for CFS/ME as a whole and with an option for a more stringent case-definition to identify the severe cases of CFS/ME. Regardless of the definition used i.e. Model B or D, both would clearly need validating, and testing in a much larger population and also to evaluate their usefulness for comparison between studies.

6.3 Implications of results: accuracy, validity and reliability of the epidemiological case-definition

The results of this study indicate a fairly good performance of the proposed case-definition. Not only was the accuracy of case-definition reasonably good in differentiating CFS/ME patients from those with other chronic fatiguing illnesses, but the scope of the definition could also be extended to situations where there is uncertainty about which cases to exclude particularly where possible alternative explanations have been proven not to be the cause of illness.

The proposed epidemiological case-definition classified approximately:

- 92% of the less severe CFS/ME group (as described in the preceding section) accurately demonstrating good sensitivity with moderate specificity of 66% and
- 76% of the most severe CFS/ME group accurately with a good specificity of 88%.

6.3.1 Limitations on validity within the study

The findings in this report are subject to at least three limitations. Firstly, the parameters examined are based on self-reported data and is subject to recall bias. Because of practical limitations it was not possible to independently confirm with patients the information provided in the proforma by GPs. Thus, the study relied on self-reported data provided by 70 GPs and a consequence of this was incomplete data for a number of cases. This did not impact significantly on the results of the study as a sensitivity analyses indicated that cases with undecided values did not differ in analytically important ways from cases where values were present. Secondly, the sample size was relatively small (compared to large-scale, population based studies) and samples were drawn from general practice.

More importantly, the presence of CFS/ME was verified using the reviewers' judgements as the reference standard test due to the lack of a gold standard epidemiological case-definition for CFS/ME. This method is recognised as the best proxy against which epidemiological case-definitions can be assessed in the absence of a gold standard (Katz et al. 2000). The study compared agreement levels among reviewers as a form of validity. The agreement was found to be moderate among the reviewers and significant beyond statistical chance. The reviewers' opinion was thus employed as the nearest approximation for a gold standard. The study also assessed the impact of uncertainty on the outcome measure through univariate sensitivity analyses which varied the minimum and maximum threshold values or cut point for classifying cases. The resulting threshold levels were used for the gold standard and applied later in the study to compare the performance measures across the four models of the case-definition (Coggon et al. 2005).

Ascertainment bias was avoided through the use of a comprehensive structured questionnaire based on published research criteria for CFS/ME and blinding of reviewers to the GPs diagnoses and patient demographics prior to the evaluation of cases.

6.3.2 Generalisability of the results

The presentation of clinical features varied in the study sample. There were different frequencies of clinical manifestations and though cases were not assessed for symptom severity (cases were assessed for the presence or absence of CFS/ME), it was possible to observe varying disease severity within the construct as a whole as indicated by an increased prevalence of pain and other associated symptoms. Thus the different clinical patterns of illness identified in previous studies are present within the sample which suggests that the case-definition may be able to yield valid results about clinical manifestations of CFS/ME.

Generalisability of participating General Practices

The 70 GPs who participated in the study were likely to be those with an interest in the area; hence it was likely that they were less conservative in diagnosing chronic fatiguing illnesses of unknown cause as CFS/ME. The accuracy of clinical diagnosis may not reflect the true practice of majority of GPs in the UK. Although the study sample may not be necessarily representative of the total general practice population, the practices involved were representative of the national picture (see section 5.1 for practice locations).

Overall, it can be inferred from the results that the approach taken in constructing the epidemiological case-definition model provides accurate information across the broad construct of CFS/ME by its ability to predict it and detect changes at higher threshold levels in this study. It also provides reliable information (as indicated by the results of inter-rater reliability) and has demonstrated that is a feasible model which can be implemented to facilitate epidemiological studies.

6.4 The epidemiological case-definition parameters

6.4.1 Mandatory and supportive criteria

The preliminary univariate analysis identified 14 criteria as commonly occurring features of CFS/ME. Following discriminant analysis, three identical parameters emerged as the predictors of CFS/ME group membership (a reduction in activity to less than 50% of the patient's premorbid activity, severe disabling fatigue affecting physical and mental functioning and muscle discomfort or myalgia, across the four threshold levels and formed the mandatory criteria.

The parameters which were significantly associated with the CFS/ME group (as determined by the SBV procedure) were classified as supportive criteria such as post exertional malaise, swollen lymph nodes and myalgia, flu-like symptoms (sore throat, mild fever and chills), painful cervical or axillary lymph nodes and muscle pain, multijoint pain; migratory arthralgia without joint swelling and redness, generalised muscle weakness, generalised headaches and migraine. The SBV method demonstrated that an increasing number of symptoms (as observed by the minimum number of positive responses to 14 questions) were required for CFS/ME case-classification across the four threshold levels and these formed the cut points subsequently used for the decision rule of each model.

Though the criterion of a reduction in activity to less than 50% of the patient's premorbid activity is a subjective parameter (as was majority of the criteria assessed in this study), it was the single most predictive and important variable in each model. These results are thus in accordance with several studies which suggest that the assessment of the physical functional status of CFS/ME patients can aid in distinguishing it from other chronic fatiguing illnesses (Buchwald et al. 1996). Such studies also highlighted that CFS/ME patients have significantly reduced physical activity that could worsen fatigue Afari & Buchwald 2003). However this area needs to be further developed to identify proper measures for assessing physical functional status.

Other studies have also shown that the estimated percentage decrease in activity due to fatigue, in comparison to the pre morbid activity levels, is an important predictor of CFS/ME and that other main predictors of CFS/ME case-definition membership are factors representing musculoskeletal symptoms, infection related symptoms of feverishness, sore throat, and tender lymph nodes symptoms (Brimacombe, Helmer & Natelson 2002).

Another important finding in this study was that though substantial functional impairment as an indicator of functional status and cognitive disorders were amongst the supportive criteria, they did not form a part of the three strongest predictors of CFS/ME contrary to suggestions made by some researchers. Further, sleep disorders though prevalent in the study population, were not significantly associated with or predictive of CFS/ME group membership and therefore not recognised as either mandatory or supportive criteria. This was not in accordance with the clinical research definitions (Holmes, Fukuda and Oxford) where sleep disorders feature as minor criteria and in the Canadian clinical case-definition which stipulates that 'sleep disturbance is a principal feature of CFS/ME. Other differences between the clinical research definitions and the proposed case-definition model have already been highlighted in section 5.7 of this thesis.

Substantial functional impairment, which was listed as a major criterion in the Fukuda case-definition, though correlated with a reduction in activity to less than 50% of the patient's premorbid activity, also was not a significant factor in any of the discriminant functions.

6.4.2 Comorbid and psychiatric illnesses

The decision to include or exclude cases with either anxiety disorder or depression or both conditions when present in a patient varies by case-definition. The findings suggest that at higher thresholds (C and D) the models were less likely to contain features of overlapping and psychiatric illnesses and comorbidities. Thus, the

combination of functional impairment, musculoskeletal and fatigue symptoms could predict CFS/ME as long as there were no associations with anxiety disorder in the four models and depression in models B, C and D. Both conditions are indicators of some psychiatric illnesses and were found to be major predictors for non-CFS/ME membership in these study models.

The Fukuda definition stipulates that the presence of depression and anxiety disorders do not exclude a person from the diagnosis of CFS/ME. However, this study in contrast found that at level I, anxiety disorder was a strong predictor of non-CFS/ME group membership. The findings also suggested depression as a strong individual predictor of the non-CFS/ME group, but more so when combined with anxiety disorder i.e. concurrent at levels II, III and IV.

This indicates that contrary to the findings from other studies that suggest depression occurs commonly in the CFS/ME population (Wessely et al. 1996), its co-existence with other psychiatric related disorders such as anxiety; provides strong justification for the exclusion of a case from the diagnosis of CFS/ME as found in this study. The proposed definition may thus distinguishes the symptoms of CFS/ME from those due to a psychiatric explanation.

Janal et al. (2006) reported that depression and anxiety, while frequently present, are not more prevalent in any particular CFS/ME subtype (Janal et al. 2006). These results thus confirm their findings and support other research which disprove the suggestion of a relationship between CFS/ME and depression, (Short, McCabe & Tooley 2002/6, Vercoulen et al. 1998, Wessely, Hotopf & Sharpe 1998) but refute findings which maintain that depressive disorders are perpetuating factors of CFS/ME.

In addition to distinguishing CFS/ME symptoms from those due to a comorbid psychiatric illness, the proposed definition distinguished between CFS/ME and fibromyalgia at threshold level IV. There was no significant association at this level thus confirming studies that suggest that CFS/ME and fibromyalgia are different but related conditions (Sullivan, Smith & Buchwald, 2002).

6.4.3 Exclusionary conditions

As the focus of the study was on the correct classification of CFS/ME cases, exclusionary criteria were not studied in great depth. However, to avoid limiting the interpretation of results and to assess the impact of exclusionary criteria on the performance of the models, most of the analyses performed in the study checked the impact of including and excluding the cases with possible alternative medical or psychiatric illnesses as defined by the clinical research definitions.

Although eliminating these cases from the discriminant model classifier had a minimal impact on the overall accuracy of the classification, the discriminant classifier selected one or more exclusionary criteria as strong predictors of the non-CFS/ME group across the four thresholds. As a result, the proposed definition included a requirement for the exclusion of cases with alternate explanations for the illness. Other performance measures did not alter significantly as the sensitivities of the models remained within reasonable limits of the confidence interval ranges. Thus it was possible to evaluate the efficacy of the case-definition algorithm at the four levels i.e. how well it performed under ideal conditions. By including all the cases, it was also possible to assess the effectiveness of the proposed definition in an unselected population.

However when exclusionary conditions were included in the sensitivity analyses involving the different clinical research case-definitions, they had a noticeable impact on the performance of these clinical definitions. Upon exclusion of the cases, the sensitivity of across the threshold levels was lowered whilst specificity improved. Therefore studies using these definitions need to be interpreted not only on the basis of major and minor criteria but also in light of the exclusionary criteria.

The implication of this finding is that substantial numbers of CFS/ME cases with either mild or severe symptoms or concurrent illnesses would be excluded during surveillance activities using the current tools where too many unproven exclusionary criteria are applied. This implication can be related to another study which found that exclusionary conditions listed in clinical research definitions did not always cause fatigue

thereby resulting in the exclusion of potential CFS/ME patients in non-clinical settings where it was not possible to accurately determine the nature of fatigue in relation to concomitant illness (Reyes et al. 2003).

6.5 Assessment of GPs diagnoses

Besides the main objective of developing an epidemiological case-definition, the study also revealed how competent GPs were at diagnosing CFS/ME. The gold standard against which the GPs diagnoses was assessed was at the lowest threshold and thus highly sensitive (level).

The results showed that the diagnostic accuracy of the 70 GPs who took part in the study compared to the gold standard was 67.8% (level I). In addition, for every 10 patients diagnosed by the GPs as having CFS/ME at this level, approximately 8 of these had the condition.

In comparison to the Canadian clinical case-definition which is a highly specific definition or threshold level IV (as applied in this study), approximately four (4) of every 10 patients diagnosed as having CFS/ME by the GPs had the condition. This either suggests that there is an over diagnosis of CFS/ME in primary care or it may be an indication of a lower threshold for diagnosis by the GPs compared with the gold standard and the Canadian definition.

While very few studies have evaluated the ability of GPs to diagnose CFS/ME correctly, other studies examining GPs attitudes and knowledge of CFS/ME have shown that a significant proportion of GPs (48%) do not feel confident diagnosing CFS/ME (Bowen et al. 2005). Although this may explain in part, the level of inaccuracy of GPs diagnosis, the GPs in this study were not conservative in making the diagnosis. These results may be significant in evaluating training needs of GPs in the UK.

6.6 *Further explanation on the limitations of the study*

It is recognised that there some limitations to the study methods which may influence the accuracy and validity of the study results as mentioned in previous sections. These are further described below.

6.6.1 Biases relating to the GPs and the study participants

The data were collected by GPs in a clinical setting thus results may be skewed because the study sample is of patients who have seen a doctor, rather than a random sample of the population as a whole. And because the data for the study was not obtained directly from individual study participants i.e. the patients, this further complicated analyses of the results due to missing data. It was also not possible to establish the correctness of the data which could be a source of ascertainment bias.

Other possible selection bias might exist since the GPs' decision to participate may have been influenced by their interest and knowledge of the area of study. It is likely that those GPs with substantial knowledge of CFS/ME and experience in its diagnosis were more comfortable and willing to spend time responding to the questionnaires than those without, thus impacting on the representativeness of the GP sample.

The study title may have also influenced the GPs selection of patients. An indirect indication for this was because of the over diagnosis of CFS/ME in the patient study group. CFS/ME or a related illness was given as the provisional diagnosis by majority of the GPs in more than half of the cases. Though the inclusion criteria required patients with unexplained chronic fatigue of at least six months, it is probable that some GPs opted out of the study because they did not have patients with CFS/ME as the study titled was related to the development of a case-definition for CFS/ME even though they could have had patients with unexplained chronic fatigue of six (6) months.

In addition, GPs may have accurately recalled CFS/ME cases better than CF controls and also reported CFS/ME cases that resulted in severe illness than mild cases. A recall bias was thus more likely to affect results because the data was collected retrospectively and this also has implications for the representativeness of the patient sample and potentially distorts the completeness of reporting.

As indicated earlier, the accuracy of this retrospective data could not be verified, and thus the GPs' assessments were based on self-reports and therefore may well have incurred information bias.

6.6.2 Biases relating to the expert panel

Expert panel ratings based on the judgment of a single panel of four (4) reviewers' were employed as the gold standard in the study. This is because a prospective study based on laborious measurements or observations may have proven to be unfeasible due to high costs and the limited time.

The reviewers were from general practice and academic backgrounds. The first three reviewers from the CMO's working group had mainly research backgrounds whilst the additional 4th expert was a GP with a special interest in CFS/ME (not from the CMO's working group). Although the reviewers did not confer and all ratings of cases and controls were done independently, the differences in their backgrounds is a possible explanation for the diversity in the views of the reviewers particularly reviewer 2.

It was probable that selection of the reviewers and thus assessment of cases was susceptible to bias because more than half of those invited to join the expert panel from the CMO's working group refused to take part in the study.

Further, those who opted to participate each came from slightly different backgrounds and would have their opinion on what constituted a case of CFS/ME. The reviewers may have given a particular variable(s) more weight than others in assignment of cases which would also have influenced case assessment and ratings.

Some assumptions (see page 22) also determined the manner in which contrasts between cases and controls were made in the study as it was impossible to determine whether the occurrence of some symptoms preceded the inception of illness. The reviewers did not have this information and were asked to use their judgement in interpreting the vague definitions and imprecise characterisation of certain symptoms and conditions with respect to severity and time period.

These could have been responsible for the disparity in reviewers' assessment of disease status and thus presents a potential source of information (misclassification) bias in the study.

Although the study methods were based on verification of case assessment through multiple independent review and the agreement amongst reviewers was fair to moderate, this form of bias is still likely to be present. However, the moderate concordance between the reviewers supports the validity of the study methods. Other limitations to the study also exist in relation to potential 'rater bias' whereby each reviewer could have marked cases unduly high or low. However the ratings were averaged to obtain the final rating scores thereby reducing the impact of this potential bias.

6.6.3 The impact of excluding relevant symptoms and co-morbid conditions from the epidemiological case-definition

As anxiety and depression and co-morbid conditions e.g. fibromyalgia were identified as predictors of the non-CFS/ME comparison group in the discriminant analyses results, these were excluded from the epidemiological case-definition. This may be attributed to the nature of the study participants which is composed of CFS/ME cases and a non-CFS/ME comparison group (the chronic fatigue group) rather than cases and healthy controls. The chronic fatigue group was used instead of healthy controls as the aim of the study was to develop a definition that could tackle the

challenge of the difficulty in distinguishing between CFS/ME and other chronic fatiguing conditions. It is thus likely that the discriminant analytic model focused on excluding symptoms that could bias the results against the CFS/ME group thereby defining a specific subtype of CFS/ME whereby anxiety and depression (chronic fatiguing illnesses) did not fit the model in this particular study.

Another possible explanation for the exclusion of these symptoms is that the risk of bias was increased at the panel level, to the extent that CFS/ME is a heterogeneous condition and it was a single panel of four (4) persons that covered the entire assessment. This would have limited the representativeness of true cases. It is clear that anxiety and depression were important criteria in the comparison group based on the expert ratings. Thus if additional members of the expert panel had included a psychologist or psychiatrist, it is possible that such symptoms would not have been excluded from the discriminant analytic model.

If so, this implies that excluding people who meet all the requirements of the epidemiological case definition but have anxiety and depression or other known co-morbid conditions (see exclusions in the final case-definition), who otherwise would have been classified as a case, would result in incomplete case-identification. Thus the impact of excluding such criteria includes the potential for increased false negatives which bias case ascertainment, reduces the representation of the specific variations or subtypes in the CFS/ME population and distorts the final study results.

6.7 *Implications for future research and practice*

The proposed epidemiological case-definition accurately distinguished between CFS/ME cases and other debilitating cases of chronic fatigue. This should improve the consistency of case selection in epidemiological research studies. However, the case-definition needs to be validated in larger scale studies.

The possible biases described in the previous sections indicate that there is a limit to the accuracy that may be obtained from using the expert panels' judgment as the gold standard. Caution is thus recommended in applying these results to other studies especially. Further development of the study methods and results would therefore be an important goal for future research.

In addition, the study findings may have implications for the management of CFS/ME patients. Comparison of the four different models developed in this study revealed that although depression was a commonly occurring symptom of CFS/ME, the factors which explained the differences between CFS/ME cases and the non-CFS/ME comparison groups were not psychiatric in nature. This observation was also applicable to anxiety disorders, although they occurred less frequently.

.

Chapter 7: Conclusions and future perspectives

This study has attempted to provide an empirical basis for defining CFS/ME. It has proposed and justified a set of criteria for defining a case of CFS/ME which can be applied to epidemiological studies. Two threshold levels were proposed to enable the utilisation of a sensitive case-definition for CFS/ME as a whole and to allow a more specific case-definition for the identification of cases with substantial extent and severity.

The study, in addressing its specific aims, drew several conclusions outlined below.

Case-definition criteria

- Among the criteria from the various international case-definitions used in this study, several parameters were significantly different between the CFS/ME and non-CFS/ME groups. The most significant and consistent predictor of CFS/ME group membership was a reduction in activity to less than 50% of the patient's premorbid activity. Other major predictors of the CFS/ME group membership were also similar at different levels of diagnostic certainty thus demonstrating the robustness of the epidemiological case-definition.

- CFS/ME was also characterised by severe debilitating fatigue affecting physical and mental functioning and muscle discomfort or myalgia, unexplained generalised muscle weakness, swollen or painful lymph nodes, migratory arthralgia without joint swelling and redness and other supportive criteria.

- The exclusion criteria included concurrent anxiety disorder, depression and existing alternate illnesses proven to explain the CFS/ME symptoms.

- CFS/ME group membership was not significantly dependent on, or influenced by demographic variables.

- Sleep and psychiatric disorders did not feature as mandatory or supportive criteria in the proposed epidemiological case-definition model. This may have implications for clinical practice and guidelines in the management of CFS/ME where these conditions are thought to be associated with CFS/ME.

Case-definition methods and model

- The discrimination methods provided reasonably accurate estimates of prediction of CFS/ME group membership. The classical discriminant analysis approach gave an improved classification success compared with the sum of binary variables (SBV) method. Whereas the SBV method was useful in identifying the appropriate number of positive responses to a set of 14 questions which formed the supportive criteria.

The results of the discriminant analysis and the ROC curve were used to determine the best model for the case-identification. Model B emerged as the most appropriate judging by the results of the 'area under curve' of the receiver operator characteristic (ROC) curve analysis which provided further useful information for the interpretation of the results. When combined with the results of the SBV this produced a two-level epidemiological case-definition model that allowed discrimination between CFS/ME cases and the non- CFS/ME comparison group.

- The usefulness of an epidemiological case-definition lies in its ability to distinguish between affected persons and other groups. The case-definition could thus fulfil the requirement for a highly sensitive definition when the purpose is to identify all individuals with CFS/ME as a whole, or those with mild to moderate illness severity. The first level of the proposed case-definition would thus suit the requirements for a monitoring or surveillance tool when the aim is to estimate the magnitude of CFS/ME as a public health problem. At this level, the case-definition listed seven (7) criteria, with the

requirement to fulfil three (3) mandatory criteria and any four (4) mandatory criteria to be classified a case.

- The results indicate that the two levels proposed for the case-definition lie on a continuum of severity however further work is needed to validate this finding which may be useful in aetiological studies as it may allow researchers to assess if the two levels are aetiological distinct.

- The study results supported the validity of the methods employed and the case-definition model as a practical tool for CFS/ME epidemiological purposes. Although much research is still needed in this area, the proposed case-definition would be of benefit to those who wish to use it as a basis for epidemiological research for prevalence assessment of CFS/ME in the general population. It would facilitate data collection in different settings and enhance comparability of studies.

- The study was based on a clinical (general practice) population and thus the sample size is relatively small when compared to general population studies. This definition should be validated on other levels, including a larger and more diverse population sample to increase its generalisability as more severely affected patients such as in acute care or attending CFS/ME specialist clinics as well as those managed by complementary and alternative medicines practitioners were not included in the research.

Although the statistical approaches employed in this report may be used to partially estimate the standard deviation of CFS/ME prevalence estimates (when applied to past studies), the approaches account only for the possible uncertainty (existing as a result of the small sample size) in the estimates of CFS/ME in the general practice population (as applied this study).

- Application of the alternative definitions showed that the results were highly sensitive to variations in definitions. When the current clinical research case-definitions were applied to the gold standard review, the case-definition with the highest sensitivity was the Oxford case-definition, followed by the Australian definition, Fukuda- CDC 1994, and Holmes- CDC 1988 definition. The performance of these definitions was sensitive to exclusionary criteria. The wide range of sensitivities observed during this procedure necessitates standardisation of these alternative case-definitions in order to facilitate the comparability of epidemiological data from past studies using these definitions and to provide more accurate estimate of the prevalence of CFS/ME.

- Future educational initiatives for GPs should take into account the diagnosis of CFS/ME in general practice and to identify other areas in which GPs could be trained and supported more effectively.

Future work

- The two-level epidemiological case-definition model demonstrated good sensitivity, specificity and accuracy but a slightly lower negative predictive value at the first level which could be improved by validating the epidemiological case-definition in different settings. The definition was also robust to changes in the application of exclusionary criteria and demonstrated good ability to classify cases to CFS/ME and non-CFS/ME groups irrespective of the presence of exclusionary conditions as shown by the performance measures. However, further work is required in this area to define appropriate criteria for exclusion to ensure that patients with mild or severe illness are not excluded during surveillance activities particularly those whose CFS/ME symptoms are not explained by an existing alternate illness.
- External validation of the case-definition in a larger population (that is not restricted to clinical population) would limit any uncertainty that may exist about the true median and standard deviation of the distribution of CFS/ME during prevalence assessment. This would:

- Enable formal inferences to be made about the prevalence of CFS/ME
- Further improve comparability of results across different populations and aid in the interpretation of past studies undertaken using clinical research definitions in larger populations.

▪ This study has also attempted to assess the impact of clinical research definitions on estimates of prevalence. However additional research using the proposed definition is needed to develop methods to assess standard deviations (the standard or relative error) of prevalence estimates in large-scale, population-based, epidemiological studies using these clinical research definitions.

Overall study conclusions

The study produced encouraging results. In particular, a highly sensitive and accurate tool for distinguishing between CFS/ME and non-CFS/ME cases as recommended by the Medical Research Council. The proposed epidemiological case-definition would allow the collection of enough detailed information and would thus be practical for epidemiological purposes. It provides a potentially practical (useful) and well-defined measure on which to base policy recommendations.

Further, the case-definition provides new and useful information that facilitates comparison of studies undertaken with clinical research definitions and thus provides a useful alternative to these methods which were mostly theoretically rather than empirically derived.

Finally, the proposed definition takes into consideration features that were relevant to assessing functional status and disability (or severity as measured by increasing symptomatology). These measures were directly related to the likelihood ratios and positive predictive values. This could be useful in predicting patterns of help-seeking for people with CFS/ME. Proper implementation of the case-definition can thus facilitate public health needs assessment and access to care. This would in turn lead to improvements in the provision of appropriate health care services by targeting available

resources to match the level of need e.g. those with the more severe cases of CFS/ME would require different or additional access to care. This will greatly be appreciated by carers of CFS/ME patients and patients with CFS/ME.

REFERENCES

Aaron, L.A. & Buchwald, D. 2001, "A Review of the Evidence for Overlap among Unexplained Clinical Conditions.[Miscellaneous]", *Annals of Internal Medicine,* vol. 134, no. 9 (Part 2) (Supplement, pp. 868-881).

Acheson, E.D. 1959, "The clinical syndrome variously called benign myalgic encephalomyelitis, Iceland disease and epidemic neuromyasthenia", *The American Journal of Medicine,* vol. 26, no. 4, pp. 569-595.

Afari, N. & Buchwald, D. 2003, "Chronic Fatigue Syndrome: A Review", *American Journal of Psychiatry,* vol. 60, pp. 221-226.

Bagnall, A.M., Whiting, P., Richardson, R. & Sowden, A.J. 2002, "Interventions for the treatment and management of Chronic Fatigue Syndrome/Myalgic Encephalomyelitis", *Quality and Safety in Health Care.,* vol. 11, no. 3, pp. 284-288.

Bates, D.W., Buchwald, D., Lee, J., Kith, P., Doolittle, T., Rutherford, C., Churchill, W.H., Schur, P.H., Wener, M. & Wybenga, D. 1995, "Clinical laboratory test findings in patients with Chronic Fatigue Syndrome", *Archives of Internal Medicine,* vol. 155, no. 1, pp. 97-103.

Bierl, C., Nisenbaum, R., Hoaglin, D.C., Randall, B., Jones, A.B., Unger, E.R. & Reeves, W.C. 2004, "Regional distribution of fatiguing illnesses in the United States: a pilot study", *Population Health Metrics,* vol. 2, no. 1, pp. 1.

Bombardier, C.H. & Buchwald, D. 1995, "Outcome and prognosis of patients with chronic fatigue vs chronic fatigue syndrome", *Archives of Internal Medicine,* vol. 155, no. 19, pp. 2105-2110.

Bou-Holaigah, I., Rowe, P.C., Kan, J. & Calkins, H. 1995, "The relationship between neurally mediated hypotension and the chronic fatigue syndrome", *JAMA : the journal of the American Medical Association,* vol. 274, no. 12, pp. 961-967.

Bowen, J., Pheby, D., Charlett, A. & McNulty, C. 2005, "Chronic Fatigue Syndrome: a survey of GPs' attitudes and knowledge", *Family practice,* vol. 22, no. 4, pp. 389-393.

Brenner, H. & Gefeller, O. 1997, "Variation of sensitivity, specificity, likelihood ratios and predictive values with disease prevalence", *Statistics in Medicine,* vol. 16, no. 9, pp. 981-991.

Brimacombe, M., Helmer, D. & Natelson, B.H. 2002, "Clinical differences exist between patients fulfilling the 1988 and 1994 case-definitions of chronic fatigue syndrome. Journal of Clinical Psychology in Medical Settings", *Journal of Clinical Psychology in Medical Settings,* vol. 9, pp. 309-314.

Buchwald, D. 1996, "Fibromyalgia and chronic fatigue syndrome: similarities and differences", *Rheumatic diseases clinics of North America,* vol. 22, no. 2, pp. 219-243.

Buchwald, D., Cheney, P.R., Peterson, D.L., Henry, B., Wormsley, S.B., Geiger, A., Ablashi, D.V., Salahuddin, S.Z., Saxinger, C. & Biddle, R. 1992, "A chronic illness characterized by fatigue, neurologic and immunologic disorders, and active human herpesvirus type 6 infection", *Annals of Internal Medicine,* vol. 116, pp. 103-113.

Buchwald, D. & Garrity, D. 1994, "Comparison of patients with chronic fatigue syndrome, fibromyalgia, and multiple chemical sensitivities", *Archives of Internal Medicine,* vol. 154, no. 18, pp. 2049-2053.

Buchwald, D., Pearlman, T., Umali, J., Schmaling, K. & Katon, W. 1996, "Functional status in patients with chronic fatigue syndrome, other fatiguing illnesses, and healthy individuals", *The American Journal of Medicine,* vol. 101, no. 4, pp. 364-370.

Buchwald, D., Umali, P., Umali, J., Kith, P., Pearlman, T. & Komaroff, A.L. 1995, "Chronic fatigue and the chronic fatigue syndrome: prevalence in a Pacific Northwest health care system", *Annals of Internal Medicine,* vol. 123, no. 2, pp. 81-88.

Busichio, K., Tiersky, L.A., Deluca, J. & Natelson, B.H. 2004, "Neuropsychological deficits in patients with chronic fatigue syndrome", *Journal of the International Neuropsychological Society : JINS,* vol. 10, no. 2, pp. 278-285.

Carruthers, B.M., Jain, A.K., De Meirleir, K.L., Peterson, D.L., Klimas, N.G., Lemer, A.M., Bested, A.C., Flor-Henry, P., Joshi, P., Powles, A.C.P., Sherkey, J.A. & van de Sande, M.I. 2003, "Myalgic encephalomyelitis/chronic fatigue syndrome: clinical working case-definition, diagnostic and treatment protocols", *Journal of Chronic Fatigue Syndrome,* vol. 11, pp. 7-115.

CFS/ME Working Group 2002, *A Report of the CFS/ME Working Group: Report to the Chief Medical Officer of an Independent Working Group*, Department of Health, London.

Coggon, D., Martyn, C., Palmer, K.T. & Evanoff, B. 2005, "Assessing case-definitions in the absence of a diagnostic gold standard", *International Journal of Epidemiology,* vol. 34, no. 4, pp. 949-952.

Cohen, J. 1968, "Weighted kappa: nominal scale agreement with provision for scaled disagreement or partial credit.", *Psychological Bulletin,* , no. 70, pp. 213- 220.

Craig, T. & Kakumanu, S. 2002a, "Chronic fatigue syndrome: evaluation and treatment", *American Family Physician,* vol. 65, no. 6, pp. 1083-1090.

De Becker, P., McGregor, N. & De Meirleir, K. 2001, "A definition-based analysis of symptoms in a large cohort of patients with chronic fatigue syndrome", *Journal of internal medicine,* vol. 250, no. 3, pp. 234-240.

De Lorenzo, F., Hargreaves, J. & Kakkar, V.V. 1997, "Pathogenesis and management of delayed orthostatic hypotension in patients with chronic fatigue syndrome", *Clinical autonomic research : official journal of the Clinical Autonomic Research Society,* vol. 7, no. 4, pp. 185-190.

De Meirleir, K., Bisbal, C., Campine, I., De Becker, P., Salehzada, T., Demettre, E. & Lebleu, B. 2000/2, "A 37 kDa 2-5A binding protein as a potential biochemical marker for

chronic fatigue syndrome", *The American Journal of Medicine,* vol. 108, no. 2, pp. 99-105.

DeLeo, J. 1993, "*Receiver operating characteristic laboratory (ROCLAB): Software for developing decision strategies that account for uncertainty*.", *2nd International Symposium on Uncertainty Modelling and Analysis. College Park, MD: IEEE Computer Society Press.*

DeLuca, J., Johnson, S.K., Ellis, S.P. & Natelson, B.H. 1997, "Cognitive functioning is impaired in patients with chronic fatigue syndrome devoid of psychiatric disease", *Journal of neurology, neurosurgery, and psychiatry,* vol. 62, no. 2, pp. 151-155.

Demitrack, M.A. & Crofford, L.J. 1998, "Evidence for and pathophysiologic implications of hypothalamic-pituitary-adrenal axis dysregulation in fibromyalgia and chronic fatigue syndrome", *Annals of the New York Academy of Sciences,* vol. 840, pp. 684-697.

Department of Human Services, SA. 2004, *Myalgic Encephalopathy (ME) and chronic fatigue syndrome (CFS/ME): management guidelines for General Practitioners.*, Department of Human Services, SA., South Australia.

Donnay, A. & Ziem, G. 1999, "Prevalence and overlap of chronic fatigue syndrome and fibromyalgia syndrome among 100 new patients with multiple chemical sensitivity syndrome.", *Journal of Chronic Fatigue Syndrome,* vol. 5, no. 3/4, pp. 71- 80.

Dowsett, E.G., Goudsmit, E.M., Macintyre, A. & and Shepherd, C. 1994, *London Criteria for Myalgic Encephalomyelitis. In: Report from the National Task Force on Chronic Fatigue Syndrome (CFS/ME), Post Viral Fatigue Syndrome (PVFS), Myalgic Encephalomyelitis (ME), Westcare.*

Dowsett, E.G. 1992, "Conversation piece. Interview by P. D. Welsby", *Postgraduate medical journal,* vol. 68, no. 795, pp. 63-65.

Dowsett, E.G., Ramsay, A.M., McCartney, R.A. & Bell, E.J. 1990, "Myalgic encephalomyelitis--a persistent enteroviral infection?", *Postgraduate medical journal,* vol. 66, no. 777, pp. 526-530.

England, J.D., Gronseth, G.S., Franklin, G., Miller, R.G., Asbury, A.K., Carter, G.T., Cohen, J.A., Fisher, M.A., Howard, J.F., Kinsella, L.J., Latov, N., Lewis, R.A., Low, P.A. & Sumner, A.J. 2005, "Distal symmetric polyneuropathy: A definition for clinical research: Report of the American Academy of Neurology, the American Association of Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation", *Neurology,* vol. 64, no. 2, pp. 199-207.

Evans, R.H. 1978, "Inter-Bank Perceptions: A Marketing Application of Discriminant Analysis. ", *The Journal of the Operational Research Society,* vol. 29, no. 7, pp. 661-665.

Evengard, B., Schacterle, R.S. & Komaroff, A.L. 1999, "Chronic fatigue syndrome: new insights and old ignorance", *Journal of internal medicine,* vol. 246, no. 5, pp. 455-469.

Everitt, B. 1996, *The Cambridge Dictionary of Statistics in the Medical Sciences,* 1st edn, Cambridge Univ Press, New York.

Freeman, R., Komaroff, L., & Anthony M.D. 1997/4, "Does the Chronic Fatigue Syndrome Involve the Autonomic Nervous System?", *The American Journal of Medicine,* vol. 102, no. 4, pp. 357-364.

Faraone, S.V., & Tsuang, M.T. 1994. Measuring diagnostic accuracy in the absence of a “gold standard.” Am J Psychiatry 151(5):650–657.

Friedberg, F., Dechene, L., McKenzieli, M.J. & Fontanetta, R. 2000, "Symptom patterns in long-duration chronic fatigue syndrome", *Journal of Psychosomatic Research,* vol. 48, no. 1, pp. 59-68.

Fukuda, K., Straus, S.E., Hickie, I., Sharpe, M.C., Dobbins, J.G. & Komaroff, A. 1994, "The chronic fatigue syndrome: a comprehensive approach to its definition and study.

International Chronic Fatigue Syndrome Study Group", *Annals of Internal Medicine,* vol. 121, pp. 953-959.

GAO/HEHS 2000, *Chronic fatigue syndrome: CDC and NIH research activities are diverse, but agency coordination is limited.*, United States General Accounting Office, Washington, D.C.

Garson, D. 1996, 2006, *, Discriminant Function Analysis* [Homepage of Statistics Solutions, Inc.], [Online]. Available: http://www.statisticssolutions.com/discrim.htm [2006, 08/26] .

Gaudino, E.A., Coyle, P.K. & Krupp, L.B. 1997, "Post-Lyme syndrome and chronic fatigue syndrome. Neuropsychiatric similarities and differences", *Archives of Neurology,* vol. 54, no. 11, pp. 1372-1376.

Gerbert, B. & Hargreaves, W.A. 1986, "Measuring Physician Behavior.", *Medical Care,* vol. 24, pp. 838-847.

Gold, D., Bowden, R., Sixbey, J., Riggs, R., Katon, W.J., Ashley, R., Obrigewitch, R.M. & Corey, L. 1990, "Chronic fatigue. A prospective clinical and virologic study", *JAMA : the journal of the American Medical Association,* vol. 264, no. 1, pp. 48-53.

Gow, J.W., Simpson, K., Behan, P.O., Chaudhuri, A., McKay, I.C. & Behan, W.M. 2001, "Antiviral pathway activation in patients with chronic fatigue syndrome and acute infection", *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America,* vol. 33, no. 12, pp. 2080-2081.

Hand, D.J. 1983, "A comparison of two methods of discriminant analysis applied to binary data.", *Biometrics,* vol. 39, no. 3, pp. 683-694.

Hanley, J.A. & McNeil, B.J. 1982, "The meaning and use of the area under the receiver operating characteristic (ROC) curve", *Radiology,* vol. 143, pp. 29-36.

Hickie, I., Lloyd, A., Hadzi-Pavlovic, D., Parker, G., Bird, K. & Wakefield, D. 1995, "Can the chronic fatigue syndrome be defined by distinct clinical features?", *Psychological Medicine,* vol. 25, no. 5, pp. 925-935.

Holmes, G.P., Kaplan, J.E., Gantz, N.M., Komaroff, A.L., Schonberger, L.B., Straus, S.E., Jones, J.F., Dubois, R.E., Cunningham-Rundles, C. & Pahwa, S. 1988, "Chronic fatigue syndrome: a working case-definition", *Annals of Internal Medicine,* vol. 108, no. 3, pp. 387-389.

Hosmer, D.W. & Lemeshow, S. 2000, *Applied logistic regression,* John Wiley and Sons, New York, USA.

Hosmer, D.W. & Lemeshow, S. 1989, "Applied Logistic Regression", *New York, NY: John Wiley & Sons Inc,* , pp. 140-145.

Hyde, B.M., Goldstein, J.A. & and Levine, P. (eds) 1992, *The Clinical and Scientific Basis of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome*, 1st edn, Nightingale Research Foundation, Canada.

Inder, W.J., Prickett, T.C. & Mulder, R.T. 2005, "Normal opioid tone and hypothalamic-pituitary-adrenal axis function in chronic fatigue syndrome despite marked functional impairment", *Clinical endocrinology,* vol. 62, no. 3, pp. 343-348.

Institute of Medicine 2000, "Gulf War Illnesses and Recognizing New Diseases" in *Gulf War and Health: Volume 1. Depleted Uranium, Pyridostigmine Bromide, Sarin, and Vaccines*, eds. C. Fulco, C.T. Liverman & H.C. Sox, 1st edn, National Academy Press, Washington D.C., pp. 342-349.

Ismail, K., Everitt, B., Blatchley, N., Hull, L., Unwin, C., David, A. & Wessely, S. 1999, "Is there a Gulf War syndrome?", *The Lancet,* vol. 353, no. 9148, pp. 179-182.

Janal, M.N, Ciccone, D.S., Natelson B.H. 2006, “Sub-typing CFS patients on the basis of 'minor' symptoms,” *Biol Psychol*. vol.73, no. 2, pp124-31. Epub 2006 Feb 10.

Jason, L.A., Torres-Harding, S.R., Jurgens, A. & and Helgerson, J. 2004, "Comparing the Fukuda et al. criteria and the Canadian case-definition for chronic fatigue syndrome", *Journal of Chronic Fatigue Syndrome,* vol. 12, no. 1, pp. 37-52.

Jason, L.A. & and Taylor, R.R. 2002, "Applying cluster analysis to define a typology of chronic fatigue syndrome in a medically-evaluated, random community sample", *Psychology and Health,* vol. 17, no. 3, pp. 323 - 337.

Jason, L.A., King, C.P., Richman, J.A., Taylor, R.R. & Tones, S.R. 1999, "US case-definition of Chronic Fatigue Syndrome: Diagnostic and theoretical issues", *Journal of Chronic Fatigue Syndrome,* vol. 5, no. 3/4, pp. 3 - 33.

Jason, L.A., King, C.P., Taylor, R.R. & Kennedy, C. 2000, "Defining chronic fatigue syndrome: Methodological challenges.", *Journal of Chronic Fatigue Syndrome,* vol. 7, no. 3, pp. 17–32.

Jason, L.A., Torres-Harding, S.R., Taylor, R.R. & Carrico, A.W. 2001, "A comparison of the 1988 and 1994 diagnostic criteria for Chronic Fatigue Syndrome", *Journal of Clinical Psychology in Medical Settings,* vol. 8, pp. 337-343.

Jason, L.A., Helgerson, J., Torres-Harding, S.R., Carrico, A.W., & Taylor, R.R. 2003 “Variability in diagnostic criteria for chronic fatigue syndrome may result in substantial differences in patterns of symptoms and disability”, *Evaluation & the Health Professions*, vol. 26, pp. 3-22.

Jason, L.A., Corradi, K., Torres-Harding, S., Taylor, R.R. & King, C. 2005, "Chronic fatigue syndrome: the need for subtypes", *Neuropsychology review,* vol. 15, no. 1, pp. 29-58.

Jason, L.A., Richman, J.A., Friedberg, F., Wagner, L., Taylor, R. & Jordan, K.M. 1997, "Politics, science, and the emergence of a new disease. The case of chronic fatigue syndrome", *The American Psychologist,* vol. 52, no. 9, pp. 973-983.

Jason, L.A., Richman, J.A., Rademaker, A.W., Jordan, K.M., Plioplys, A.V., Taylor, R.R., McCready, W., Huang, C.F. & Plioplys, S. 1999, "A community-based study of chronic fatigue syndrome", *Archives of Internal Medicine,* vol. 159, no. 18, pp. 2129-2137.

Jason, L.A., Taylor, R.R. & Kennedy, C.L. 2000, "Chronic fatigue syndrome, fibromyalgia, and multiple chemical sensitivities in a community-based sample of persons with chronic fatigue syndrome-like symptoms", *Psychosomatic medicine,* vol. 62, no. 5, pp. 655-663.

Jason, L.A., Torres-Harding, S.R., Carrico, A.W. & Taylor, R.R. 2002/2, "Symptom occurrence in persons with chronic fatigue syndrome", *Biological Psychology,* vol. 59, no. 1, pp. 15-27.

Jason, L.A., Richman, J.A., Rademaker, A.W., Jordan, K.M., Plioplys, A.V., Taylor, R.R., McCready, W., Huang, C. & Plioplys, S. 1999, "A Community-Based Study of Chronic Fatigue Syndrome", *Archives of Internal Medicine,* vol. 159, no. 18, pp. 2129-2137.

Jason, L.A., Taylor, R.R., Kennedy, C.L., Jordan, K., Song, S., Johnson, D.E. & Torres, S.R. 2000, "Chronic Fatigue Syndrome: Sociodemographic Subtypes in A Community-Based Sample", *Evaluation the Health Professions,* vol. 23, no. 3, pp. 243-263.

Jeaschke, R., Guyatt, G.H. & Sackett, D.L. 1994a, "User's guidelines to the medical literature, III: how to use an article about a diagnostic test, A: are the results of the study valid? ", *The Journal of the American Medical Association,* vol. 271, pp. 389-391.

Jeaschke, R., Guyatt, G.H. & Sackett, D.L. 1994b, "User's guidelines to the medical literature, III: how to use an article about a diagnostic test, B: what are the results and will they help me in caring for my patients?", *The Journal of the American Medical Association,* vol. 271, pp. 703-707.

Johnson, R. A. and Wichern, D. W. (ed) 1998, *Applied Multivariate Analysis*, 4th edition edn, Prentice Hall, Englewood Cliffs, New Jersey.

Katz, J., Stock, S.R., Evanoff, B.A., Rempel, D., Moore, J.S., Franzblau, A. & Gray, R.H. 2000, "Classification criteria and severity assessment in work-associated upper extremity disorders: Methods matter", *American Journal of Industrial Medicine,* vol. 38, no. 4, pp. 369-372.

Kaur, H. & Raghava, G.P.S. 2004, "A neural network method for prediction of β-turn types in proteins using evolutionary information", *Bioinformatics,* vol. 20, no. 16, pp. 2751-2758.

Kennedy, G., Abbot, N.C., Spence, V., Underwood, C. & Belch, J.J.F. 2004/2, "The Specificity of the C D C-1994 criteria for chronic fatigue syndrome: comparison of health status in three groups of patients who fulfill the criteria", *Annals of Epidemiology,* vol. 14, no. 2, pp. 95-100.

Kirkwood, B.R. 1988, *Essentials of medical statistics,* Blackwell Scientific, Oxford.

Klecka, W.R. 1980, *Quantitative Applications in the Social Sciences #19: Discriminant Analysis,* 1st edn, Sage Publications, US.

Klimas, N.G., Salvato, F.R., Morgan, R. & Fletcher, M.A. 1990, "Immunologic abnormalities in chronic fatigue syndrome", *Journal of clinical microbiology,* vol. 28, no. 6, pp. 1403-1410.

Komaroff, A. 2000, "The Physical Basis of CFS/ME", *CFS/ME Research Review,* vol. 1, no. 2.

Komaroff, A.L., Fagioli, L.R., Geiger, A.M., Doolittle, T.H., Lee, J., Kornish, R.J., Gleit, M.A. & Guerriero, R.T. 1996, "An examination of the working case-definition of chronic fatigue syndrome", *The American Journal of Medicine,* vol. 100, no. 1, pp. 56-64.

Lachenbruch, P.A. 1975, *Discriminant Analysis,* Hafner Press, New York, NY.

Landis, J.R. 1977, "The measurement of observer agreement for categorical data.", *Biometrics,* vol. 33, pp. 159-174.

Langbehn, D.R. & Woolson, R.F. 1997, "Discriminant analysis using the unweighted sum of binary variables: a comparison of model selection methods.", *Statistics in Medicine,* vol. 16, no. 2679, pp. 2680–2700.

Lawrie, S.M. & Pelosi, A.J. 1995, "Chronic fatigue syndrome in the community. Prevalence and associations", *The British journal of psychiatry; the journal of mental science,* vol. 166, no. 6, pp. 793-797.

Linder, R., Dinser, R., Wagner, M., Krueger, G.R. & Hoffmann, A. 2002, "Generation of classification criteria for chronic fatigue syndrome using an artificial neural network and traditional criteria set", *In vivo (Athens, Greece),* vol. 16, no. 1, pp. 37-43.

Lloyd, A.R., Hickie, I., Boughton, C.R., Spencer, O. & Wakefield, D. 1990, "Prevalence of chronic fatigue syndrome in an Australian population", *The Medical journal of Australia,* vol. 153, no. 9, pp. 522-528.

Lyketsos, C.G., Lopez, O., Jones, B., Fitzpatrick, A.L., Breitner, J. & DeKosky, S. 2002, "Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment: results from the cardiovascular health study", *JAMA : the journal of the American Medical Association,* vol. 288, no. 12, pp. 1475-1483.

Manu, P., Lane, T.J. & Matthews, D.A. 1993, "Chronic fatigue and chronic fatigue syndrome: clinical epidemiology and aetiological classification", *Ciba Foundation symposium,* vol. 173, pp. 23-31; discussion 31-42.

Manu, P., Matthews, D.A. & Lane, T.J. 1988, "The mental health of patients with a chief complaint of chronic fatigue. A prospective evaluation and follow-up", *Archives of Internal Medicine,* vol. 148, no. 10, pp. 2213-2217.

Marcel, B., Komaroff, A.L., Fagioli, L.R., Kornish, R.J.,2nd & Albert, M.S. 1996, "Cognitive deficits in patients with chronic fatigue syndrome", *Biological psychiatry,* vol. 40, no. 6, pp. 535-541.

Marshall, P.S., Forstot, M., Callies, A., Peterson, P.K. & Schenck, C.H. 1997, "Cognitive slowing and working memory difficulties in chronic fatigue syndrome", *Psychosomatic Medicine,* vol. 59, no. 1, pp. 58-66.

McCrone, P., Darbishire, L., Ridsdale, L. & Seed, P. 2003, "The economic cost of chronic fatigue and chronic fatigue syndrome in UK primary care", *Psychological medicine,* vol. 33, pp. 253-261.

Medical Research Council 2003, *Report of MRC CFS/ME Research Workshop on Epidemiology*, Medical Research Council, 2003.

Michiels, V. & Cluydts, R. 2001, "Neuropsychological functioning in chronic fatigue syndrome: a review", *Acta Psychiatrica Scandinavica,* vol. 103, no. 2, pp. 84-93.

Moss-Morris, R. & Petrie, K.J. 2001, "Discriminating between chronic fatigue syndrome and depression: a cognitive analysis", *Psychological medicine,* vol. 31, no. 3, pp. 469-479.

MRC CFS/ME Research Advisory Group 2003, *CFS/ME Research Strategy*, Medical Research Council, London.

Mulrow, C.D., Ramirez, G. & Cornell, J.E.e.a. 2001, *Defining and Managing Chronic Fatigue Syndrome. Evidence Report/Technology Assessment No. 42 (Prepared by San Antonio Evidence-based Practice Center at The University of Texas Health Science Center at San Antonio under Contract No. 290-97-0012).*, Agency for Healthcare Research and Quality, AHRQ Publication No. 02-E001. Rockville (MD).

Myalgic Encephalomyelitis Research Group for Education and Support 2003, *American Association for Chronic Fatigue Syndrome (AACFS) 6th International Conference on Chronic Fatigue Syndrome, Fibromyalgia and Related Illnesses*, MERGE, U.S.

Natelson, B.H. & Lange, G. 2002, "A status report on chronic fatigue syndrome", *Environmental health perspectives,* vol. 110 Suppl 4, pp. 673-677.

Nisenbaum, R., Reyes, M., Mawle, A.C. & Reeves, W.C. 1998, "Factor analysis of unexplained severe fatigue and interrelated symptoms: overlap with criteria for chronic fatigue syndrome", *American Journal of Epidemiology,* vol. 148, no. 1, pp. 72-77.

Nisenbaum, R., Reyes, M., Unger, E.R. & Reeves, W.C. 2003, "Factor analysis of symptoms among subjects with unexplained chronic fatigue: What can we learn about chronic fatigue syndrome?", *Journal of Psychosomatic Research,* vol. in press.

O'Connell, B. & Myers, H. 2002, "Research in brief: The sensitivity and specificity of the Morse Fall Scale in an acute care setting", *Journal of Clinical Nursing,* vol. 11, pp. 134-136.

Park, S.H., Goo, J.M. & Jo, C.H. 2004, "Receiver Operating Characteristic (ROC) Curve: Practical Review for Radiologists", *Korean Journal of Radiology,* vol. 5, no. 1, pp. 11-18.

Pheby, D. 2000, *Management and Treatment of ME*, Positive Health Publications, UK.

'Portenoy R, '. 2003, *, Fatigue (chapter in) Interactive Textbook on Clinical Symptom Research*. Available: http://painconsortium.nih.gov/symptomresearch/ [2005, 08/09] .

Ramsay, M.A. 1988, *Myalgic Encephalomyelitis and Postviral Fatigue States: The Saga of Royal Free disease*, Gower Medical Publishing, London.

Ramsay, M. 1981, "Myalgic encephalomyelitis: a baffling syndrome", *Nursing mirror,* vol. 153, no. 15, pp. 40-41.

Ranawana, R. & Palade, V. 2005, *MVGen - Ensemble Learning for MCS Majority voting with a Genetic Algorithm. Internal Report, Oxford University Computing Laboratory.*

Reeves, W.C., Lloyd, A., Vernon, S.D., Klimas, N., Jason, L.A., Bleijenberg, G., Evengard, B., White, P.D., Nisenbaum, R. & Unger, E.R. 2003, "Identification of ambiguities in the 1994 chronic fatigue syndrome research case-definition and recommendations for resolution", *BMC Health Services Research,* vol. 3, pp. 25.

Reyes, M., Gary, H.E.,Jr, Dobbins, J.G., Randall, B., Steele, L., Fukuda, K., Holmes, G.P., Connell, D.G., Mawle, A.C., Schmid, D.S., Stewart, J.A., Schonberger, L.B., Gunn, W.J. & Reeves, W.C. 1997, "Surveillance for chronic fatigue syndrome--four U.S. cities, September 1989 through August 1993", *MMWR CDC Surveill.Summ.,* vol. 46, no. 2, pp. 1-13.

Reyes, M., Nisenbaum, R., Hoaglin, D.C., Unger, E.R., Emmons, C., Randall, B., Stewart, J.A., Abbey, S., Jones, J.F., Gantz, N., Minden, S. & Reeves, W.C. 2003, "Prevalence and incidence of chronic fatigue syndrome in Wichita, Kansas", *Archives of Internal Medicine,* vol. 163, no. 13, pp. 1530-1536.

Reynolds, K.J., Vernon, S.D., Bouchery, E. & Reeves, W.C. 2004, "The economic impact of chronic fatigue syndrome", *Cost Effectiveness Resource Allocation,* vol. 2, pp. 4.

Robbins, J.M., Kirmayer, L.J. & Hemami, S. 1997, "Latent variable models of functional somatic distress", *The Journal of nervous and mental disease,* vol. 185, no. 10, pp. 606-615.

Rosenberg, 1., Aronowitz, 1. & Wessely et al., 1998 2000, "Gulf War Illnesses and Recognizing New Diseases" in *Gulf War and Health: Volume 1. Depleted Uranium, Pyridostigmine Bromide, Sarin, and Vaccines*, eds. C. Fulco, C.T. Liverman & H.C. Sox, 1st edn, National Academy Press, Washington D.C., pp. 342-349.

Rothman, K.J. & Greenland, S. (eds) 1998, *Modern Epidemiology*, 2nd ed. edn, Lippincott Williams & Wilkins, Philadelphia.

Rowe, P.C. & Calkins, H. 1998/9/28, "Neurally mediated hypotension and chronic fatigue syndrome", *The American Journal of Medicine,* vol. 105, no. 3, Supplement 1, pp. 15S-21S.

Royal College of General Practitioners 2004, *General Practitioner Workload: RCGP Information Sheet No3*, Royal College of General Practitioners, UK.

Scadding, J.G. 1996. “Essentialism and nominalism in medicine: Logic of diagnosis in disease terminology”, *Lancet* 348 vol. 9027, pp. 594–596.

Short, K., McCabe, M. & Tooley, G. 2002/6, "Cognitive functioning in Chronic Fatigue Syndrome and the role of depression, anxiety, and fatigue", *Journal of Psychosomatic Research,* vol. 52, no. 6, pp. 475-483.

Slotkoff, A.T., Radulovic, D.A. & Clauw, D.J. 1997, "The relationship between fibromyalgia and the multiple chemical sensitivity syndrome", *Scandinavian journal of rheumatology,* vol. 26, no. 5, pp. 364-367.

Solomon, L. & Reeves, W.C. 2004, "Factors influencing the diagnosis of chronic fatigue syndrome", *Archives of Internal Medicine,* vol. 164, no. 20, pp. 2241-2245.

SPSS, I. 2005, *SPSS Base 14.0 System User's Guide,* SPSS, Inc., Chicago, IL.

Sullivan, P.F., Smith, W. & Buchwald, D. 2002, "Latent class analysis of symptoms associated with chronic fatigue syndrome and fibromyalgia", *Psychological medicine,* vol. 32, no. 5, pp. 881-888.

Taylor, R.R., Jason, L.A. & and Schoeny, M.E. 2001, "Evaluating latent variable models of functional somatic distress in a community-based sample", *Journal of Mental Health,* vol. 10, no. 3, pp. 335- 349.

The Royal Australasian College of Physicians Working Group 2002, "Chronic fatigue syndrome: Clinical Practice guidelines 2002", *Medical Journal of Australia,* vol. 176, no. 8 Suppl, pp. S17-S55.

Torpy, D.J., Bachmann, A.W., Gartside, M., Grice, J.E., Harris, J.M., Clifton, P., Easteal, S., Jackson, R.V. & Whitworth, J.A. 2004, "Association between chronic fatigue syndrome and the corticosteroid-binding globulin gene ALA SER224 polymorphism", *Endocrine research,* vol. 30, no. 3, pp. 417-429.

U.S. DHHS-CDC 1998, *Principles of Epidemiology,* 2nd edn, U.S. Department Of Health And Human Services, Public Health Service, Centers for Disease Control and Prevention, Atlanta.

Van Schalkwyk, J. 2003, 10/13-last update*, The magnificent ROC (Receiver Operating Characteristic curve)*. Available: http://www.anaesthetist.com/mnm/stats/roc [2006, 08/26] .

Vercoulen, J.H., Swanink, C.M., Galama, J.M., Fennis, J.F., Jongen, P.J., Hommes, O.R., van der Meer, J.W. & Bleijenberg, G. 1998, "The persistence of fatigue in chronic fatigue syndrome and multiple sclerosis: development of a model", *Journal of psychosomatic research,* vol. 45, no. 6, pp. 507-517.

Walsh, C.M., Zainal, N.Z., Middleton, S.J. & Paykel, E.S. 2001, "A family history study of chronic fatigue syndrome", *Psychiatric genetics,* vol. 11, no. 3, pp. 123-128.

Wegman DH, Woods NF, Bailar JC. 1997. Invited commentary: How would we know a Gulf War syndrome if we saw one? *American Journal of Epidemiology,* vol. 146, no.9, pp. 704–711; discussion 712.

Wessely, S., Chalder, T., Hirsch, S., Wallace, P. & Wright, D. 1997, "The prevalence and morbidity of chronic fatigue and chronic fatigue syndrome: a prospective primary care study", *American Journal of Public Health,* vol. 87, no. 9, pp. 1449-1455.

Wessely, S., Chalder, T., Hirsch, S., Wallace, P. & Wright, D. 1996, "Psychological symptoms, somatic symptoms, and psychiatric disorder in chronic fatigue and chronic fatigue syndrome: a prospective study in the primary care setting", *American Journal of Psychiatry,* vol. 153, no. 8, pp. 1050-1059.

Wessely, S., Hotopf, M. & Sharpe, M. 1998, "Chronic fatigue and its syndromes", .

Whistler, T., Unger, E.R., Nisenbaum, R. & Vernon, S.D. 2003, "Integration of gene expression, clinical, and epidemiologic data to characterize Chronic Fatigue Syndrome", *Journal of Translational Medicine,* vol. 1, no. 1, pp. 10.

Williams, R. & Wright, J. 1998, "Health needs assessment: Epidemiological issues in health needs assessment", *British Medical Journal,* vol. 316, no. 7141, pp. 1379-1382.

World Health Organisation 2003, 03/06/2003-last update*, International Classification of Diseases version 10* [Homepage of World Health Organisation], [Online]. Available: http://www3.who.int/icd/vol1htm2003/fr-icd.htm [2006, March/23].

Zamora, J., Abraira, V., Muriel, A., Khan, K.S. & Coomarasamy, A. 2006, "Meta-DiSc: a software for meta-analysis of test accuracy data", *BMC Medical Research Methodology,* vol. 6, pp. 31.

APPENDICES

Appendix A GP Letter

University of the West of England
BRISTOL

Faculty of Applied Sciences
Frenchay Campus,
Coldharbour Lane,
Bristol, BS16 1QY

Dear Doctor,

The development of an epidemiological case-definition for Chronic Fatigue Syndrome.

I am conducting research on Chronic Fatigue Syndrome (CFS/ME) with aim of developing an epidemiological case-definition for CFS/ME under the supervision of <<…supervisors' details..>> In order to assist the research, I am sending out proformas to General Practitioners in England to complete on chronic fatigue and its associated symptoms as manifested in primary care.

The information provided through the proformas will be a starting point for the health needs assessment for CFS/ME patients in the UK. A study reference number is assigned to each proforma so we can identify those who have responded. This is to reduce the cost of follow-up and to eliminate the disruption of follow-up for those who have returned the proformas.

We are aware that you have a heavy workload; however, your response is very important to the success of this study and we would be most grateful for your help in assisting us with this research. Enclosed is some background information about this study and thank you very much for reading the information sheet.
Please complete the consent form and proformas and return them in the enclosed freepost envelope. Any information returned will be treated in total confidence. (If you do not wish to take part please return the proforma and forms using the enclosed envelope).

If you have any queries regarding this study, please do not hesitate to contact me on 07762715268. Postal details and email address are also given below:

Tolu Osoba
Faculty of Applied Sciences
University of the West of England, Frenchay Campus
Bristol BS16 1QY
Email: Tolulope2.osoba@uwe.ac.uk

Yours sincerely,

Tolu Osoba (BDS, MSc.)

Appendix B GP Thank you letter

University of the West of England
BRISTOL

Faculty of Applied Sciences,
Coldharbour Lane,
Bristol, BS16 1QY

Dear Doctor,

Re: The Development of an Epidemiological case-definition for Chronic Fatigue Syndrome (CFS/ME)

Thank you very much for completing and returning the proforma for the research into the epidemiological case-definition for CFS/ME. The information provided will be of great value to our study.

Your cooperation in this research project is greatly appreciated.

With kind regards,

Yours sincerely,

Tolu Osoba (BDS, MSc.)

Appendix C General Practice Information Sheet

INFORMATION SHEET

THE DEVELOPMENT OF AN EPIDEMIOLOGICAL CASE-DEFINITION FOR CHRONIC FATIGUE SYNDROME (CFS/ME)

Dear Doctor

'You are being invited to take part in a research study involving the development of an epidemiological case-definition for Chronic Fatigue Syndrome (CFS/ME). This research has ethical approval from the South West Multi-centre Research Ethics Committee.
Before you make a decision, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. If there is anything that is not clear or if you would like more information, please feel free to ask.

What is the purpose of the study?
Chronic fatigue syndrome, or CFS/ME, is a debilitating and complex disorder characterised by profound fatigue that is not improved by bed rest and that may be worsened by physical or mental activity (CFIDS Association of America, 2001). It is associated with several symptoms which include fevers, pharyngitis, musculoskeletal pain, sleep disturbances, impaired concentration, depression and headaches.
There are no diagnostic tests that can validate its diagnosis, no pathognomonic medical characteristic that is common to all patients, and no defined treatment that alleviates the symptoms for all patients" (IOM, 1997).
Persons with CFS/ME most often function at a substantially lower level of activity than they were capable of before the onset of illness. In addition, there are also reports of various non-specific symptoms amongst CFS/ME patients, including weakness, muscle pain, impaired memory and/or mental concentration, insomnia and post-exertional fatigue lasting more than 24 hours.
There evidence that CFS/ME affects all racial and ethnic groups, people of differing age-groups and social economic background and both sexes. Recent longitudinal studies suggest that some persons affected by CFS/ME improve with time but that most remain functionally impaired for several years. The debilitating nature of the condition reduces the quality of life in most patients with CFS/ME.
The criteria for measuring CFS/ME are thus important and currently existing criteria are 'ambiguous' and underestimate the prevalence of CFS/ME in the general population.
It is therefore imperative to develop a set of standard criteria which will constitute an epidemiological case-definition. This would ensure that such criteria are applied consistently, regardless of where of when it occurred and who identifies it. This will provide an empirical basis to enable previous epidemiological work, undertaken using clinical research definition, to be evaluated and put in context.
It is anticipated the study would facilitate epidemiological research both descriptive and analytical into the public health burden of CFS/ME.

Do I have to take part?
It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect you in anyway.

What will happen to me if I take part?

The proposed duration of the study is 36 months but you will only be contacted between the sixth and twelfth months of the study. A checklist designed as a proforma will be sent to you for completion for each of the patients presenting with CFS/ME. This checklist consists of criteria derived from the different case-definitions for Chronic Fatigue Syndrome (CFS/ME).
You will be contacted mainly by post and you will not need to travel.

What are the possible disadvantages and risks of taking part?
I am not aware of any possible disadvantages or risks of taking part in this study

What are the possible benefits of taking part?
The performance of this study should enhance CFS/ME research and this may provide answers to a large number of unanswered questions in the prevention, diagnosis and treatment of the condition.

What if new information becomes available?
Sometimes during the course of a research project, new information becomes available about the research which may affect your decision to remain in the study. If this happens, you will be informed about it and arrangements will be made to discuss with you whether you want to continue in the study. If you decide to continue in the study you will be asked to sign an updated consent form.

Will my taking part in this study be kept confidential?
If you consent to taking part in the research the, your name and address will not be disclosed outside the University of West England. All information collected from you during the study will be kept strictly confidential. Information obtained in the study will not be used other than for the purposes stated. It will not be used in anyway that will affect your work.

What will happen to the results of the research study?
The results of the study will be submitted for publication within a year of completion. A copy of the results will be made available through the Faculty of Applied Sciences, University of the West of England. You will not be identified in any report/publication.

Who is organising the research?
The research is organised by the Faculty of Applied Sciences, University of West of England.

Contact for Further Information
Tolulope Osoba
Faculty of Applied Sciences
University of the West of England, Frenchay Campus,
Coldharbour Lane, Bristol BS16 1QY.
Telephone: 07762715268
Email: tolulope2.osoba@uwe.ac.uk

This research is being undertaken to fulfil partial of the requirements for a Doctor of Philosophy degree and I would like to thank you for considering taking part in this study.

N.B. A copy of this information sheet and the signed consent form will be given to you to keep.

Appendix D Consent Form

CONSENT FORM

Title of Project:

The Development of an Epidemiological Case-definition for Chronic Fatigue Syndrome (CFS/ME)

Name of Researcher: Tolulope Osoba

Please initial boxes

1. I confirm that I have read and understand the attached information sheet (version 2, dated 20th May 2004) on this project and have been given a copy to keep. I have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason. ☐
3. I know how to contact the researcher if I need to. ☐
4. I agree to take part in the above study. ☐

Name of GP____________________ Date_________________ Signature_______________

Appendix E Proforma

Guidance Notes for the completion of this form

CHRONIC FATIGUE SYNDROME/ MYALGIC ENCEPHALOMYELITIS (CFS/ME) STUDY.

The proforma takes **10-15 minutes** to complete. It would be helpful if you could answer the following questions for **'existing'** patient presenting with a complaint of unexplained chronic fatigue.
The questions are indicated by a list of symptoms and diseases compiled from the different case-definitions of CFS/ME (case-definitions enclosed). Please select criteria based on your professional knowledge of the symptoms or disease within the list. The symptoms and diseases selected should have presented after the onset of chronic fatigue.

How to answer

- Just tick or put a cross in the box on the right of the appropriate answer as shown below e.g. if the answer is red
  Yellow ☐ blue ☐ red ☒ green ☐
- All information will be treated as strictly confidential
- It would be helpful if the form could be completed during consultation.
- Please return the proforma to me in the freepost envelope provided.

If you have further questions please do not hesitate to contact me on 07762715268 or via email at tolulope2.osoba@uwe.ac.uk

Thank you for your help.

Tolu Osoba.

N.B. Please return by

Appendix F Case-definitions for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis

Table 68 Case-definitions for Chronic Fatigue Syndrome

Criteria	**CDC 1988**	**CDC 1994**	**Australian 1990**	**Oxford 1991 (includes criteria for Post Infectious Fatigue Syndrome-PIFS)**	**Canadian2003**
Principal symptoms	Debilitating fatigue not relieved by bed rest	Severe disabling fatigue not relieved by rest	Chronic persisting or relapsing fatigue	- Severe disabling fatigue affecting physical and mental functioning present for >50% of the time - Infection at onset or presentation corroborated by laboratory evidence	Persistent or recurrent physical or mental fatigue
Minimum duration of fatigue or illness	6 months	6 months	6 months	6 months	6 months
Functional impairment	50% decrease in activity	Substantial	Significant disruption of usual daily activities	Disabling	50% decrease in activity
Cognitive/ neuropsychiatric symptoms	May be present	May be present	Required	Mental fatigue required	Required
Other symptoms	8 required	4 required	Not specified	Not required, but other symptoms may be present, particularly myalgia, mood and sleep disturbance	2 or more required

.

	Neuropsychologic complaints (one or more of the following: photophobia, transient visual scotomata, forgetfulness, excessive irritability, confusion, difficulty thinking, inability to concentrate, depression)	Substantial impairment in short-term memory or concentration	Neuropsychiatric dysfunction including impairment of concentration evidenced by difficulty in completing mental tasks which were easily accomplished before the onset of syndrome. New onset of short term memory impairment		- Confusion, impairment of concentration and short-term memory consolidation, disorientation, difficulty with information processing, categorizing and word retrieval, and perceptual and sensory disturbances. Ataxia, muscle weakness and fasciculations, photophobia& hypersensitivity to noise and/or emotional overload. - At least 1 symptom from 2 of the following categories:- autonomic, neuroendocrine and/or immune manifestations.
	Sore throat	Sore throat			Recurrent sore throat with or without faucial injection may be present
	Painful lymph nodes in the anterior or posterior cervical or axillary distribution	Tender lymph nodes			Tender lymphadenopathy in the cervical, axillary inguinal or other regions may be present.
	Muscle discomfort or myalgia	Muscle pain			Myalgia
		Multi-joint pain without swelling or redness			Migratory arthralgia without joint swelling may be experienced

.

	Generalized headaches (of a type, severity, or pattern that is different from headaches the patient may have had in the premorbid state).	Headaches of a new type, pattern or severity			Headaches of new type, pattern or severity.
	Sleep disturbance (hypersomnia or insomnia).	Unrefreshing sleep			Sleep dysfunction
	Prolonged (24 hours or greater) generalized fatigue from levels of exercise that would have been easily tolerated in the patient's premorbid state.	Post-exertional malaise lasting more than 24 hours.			Post-exertional malaise and/or fatigue.
	Mild fever (oral temperature 37.5-38.6 ^{0}C) or chills.				
	Unexplained generalized muscle weakness.				
	Description of the main symptom complex as initially developing over a few hours to a few days.				

.

					New sensitivities to food, medications and/or various chemicals may be present.
New onset	Required	Required	Not required	Required	Required
Medical exclusions	Extensive list of known physical causes: Malignancy, autoimmune disease, localized infection e.g. occult abscess; chronic or sub acute bacterial disease e.g. endocarditis, Lyme disease or TB; fungal disease e.g. histoplasmosis, blastomycosis, or coccidioidomycosis and parasitic disease e.g. toxoplasmosis, amebiasis, giardiasis or helminthic infestation; HIV infection-related disease, chronic inflammatory disease e.g. sarcoidosis, Wegener granulomatosis or chronic hepatitis; neuromuscular disease e.g. multiple sclerosis or myasthenia gravis; endocrine disease e.g. hypothyroidism, Addison disease, Cushing syndrome, diabetes mellitus; side effects of a chronic medication or other	Exclude clinically important conditions	Known physical causes	Exclude active, unresolved, or suspect disease likely to cause fatigue e.g. anaemia – – Psychotic, melancholic, or bipolar depression (but not uncomplicated major depression) – Psychotic disorders – Dementia – Anorexia or bulimia nervosa .	Active disease processes that explain most of the major symptoms of fatigue, sleep disturbance, pain, and cognitive dysfunction. Addison's disease, Cushing's Syndrome, hypothyroidism, hyperthyroidism, iron deficiency, other treatable forms of anaemia, iron overload syndrome, diabetes mellitus, and cancer. Treatable sleep disorders such as upper airway resistance syndrome and obstructive or central sleep apnea; rheumatological disorders such as rheumatoid arthritis, lupus, polymyositis and polymyalgia rheumatica; immune disorders such as AIDS; neurological disorders such as multiple sclerosis (MS), Parkinsonism, myasthenia gravis and B12 deficiency; infectious diseases such as tuberculosis, chronic hepatitis, Lyme disease.

.

	toxic agent e.g. chemical solvent , pesticide or heavy metal; or other known or defined chronic pulmonary, cardiac, gastrointestinal, hepatic, renal, or haematologic disease.				
Psychiatric exclusions	New onset or history of: anxiety disorder, depressive disorder including endogenous depression and bipolar disorder, schizophrenia, substance abuse, chronic use of major tranquilizers, lithium or antidepressive medications.	Melancholic (severe, major) or psychotic depression, substance abuse, bipolar disorders, eating disorder, schizophrenia, dementia, delusional disorders.	Psychosis, bipolar disorder, substance abuse, eating disorder	Psychosis, bipolar disorder, eating disorder, organic brain disease, substance abuse. Other psychiatric disorders (including depressive illness, anxiety disorders, and hyperventilation syndrome) are not necessarily reasons for exclusion	Primary psychiatric disorders and substance abuse.

.

Version 2

Appendix G **<u>CFS/ME Study- Proforma</u>**

Study Reference Number (SRN)

The Development of an Epidemiological Case-definition for Chronic Fatigue Syndrome/ Myalgic Encephalomyelitis

UWE BRISTOL University of the West of England

<u>Please complete the underlying checklist by ticking the boxes for existing cases of chronic fatigue of at least six months</u>

Symptoms	**yes**	**no**	**don't know**	**Other Diseases**	**yes**	**no**	**don't know**
Debilitating fatigue not relieved by bed rest	☐	☐	☐	Anaemia	☐	☐	☐
Chronic persisting or relapsing fatigue	☐	☐	☐	Addison's disease	☐	☐	☐
Severe disabling fatigue affecting physical and mental functioning	☐	☐	☐	Cushing's Syndrome	☐	☐	☐
Infection at onset or presentation corroborated by laboratory evidence	☐	☐	☐	Hyperthyroidism	☐	☐	☐
Forgetfulness	☐	☐	☐	Hypothyroidism	☐	☐	☐
Substantial functional impairment	☐	☐	☐	Hashimoto's Disease	☐	☐	☐
50% decrease in activity	☐	☐	☐	Diabetes mellitus	☐	☐	☐
Significant disruption of usual activities	☐	☐	☐	Cancer	☐	☐	☐
Functional impairment that can be described as disabling	☐	☐	☐	Upper airway resistance syndrome	☐	☐	☐
Presence of cognitive or neuropsychiatric symptoms	☐	☐	☐	Obstructive or central sleep apnea	☐	☐	☐
Mental fatigue	☐	☐	☐	Iron overload syndrome	☐	☐	☐
Photophobia	☐	☐	☐	Hyperventilation syndrome	☐	☐	☐
Transient visual scotomata	☐	☐	☐	Interstitial Cystitis	☐	☐	☐
6 months minimum duration of fatigue or illness	☐	☐	☐	Fungal disease e.g. histoplasmosis or coccidioidomycosis	☐	☐	☐
Excessive irritability	☐	☐	☐	Parasitic disease e.g. toxoplasmosis or other helminthic infestation	☐	☐	☐
Muscle pain, multi-joint pain without swelling or redness	☐	☐	☐	Other infectious diseases e.g. HIV infection, chronic hepatitis	☐	☐	☐
Inability to concentrate	☐	☐	☐	Psychosis	☐	☐	☐
Depression	☐	☐	☐	Vitamin B12 deficiency	☐	☐	☐
Sore throat	☐	☐	☐	Anxiety disorder	☐	☐	☐
Substantial impairment in short-term memory or concentration	☐	☐	☐	Depressive disorder including endogenous depression	☐	☐	☐
Painful cervical or axillary lymph nodes	☐	☐	☐	Bipolar disorder	☐	☐	☐
Swollen lymph nodes	☐	☐	☐	Schizophrenia	☐	☐	☐
Muscle discomfort	☐	☐	☐	Substance abuse	☐	☐	☐
Migratory arthralgia without joint swelling or redness	☐	☐	☐	Melancholic (severe, major) or psychotic depression	☐	☐	☐
Myalgia	☐	☐	☐	Eating disorder	☐	☐	☐
Difficulty thinking	☐	☐	☐	Dementia	☐	☐	☐
Generalised headaches (of a type, severity, or pattern that is different from headaches the patient may have had in the premorbid state)	☐	☐	☐	Delusional disorders	☐	☐	☐
Sleep disturbance (hypersomnia or insomnia or unrefreshing sleep)	☐	☐	☐	Neurological disorders e.g. multiple sclerosis (MS), Parkinsonism, Myasthenia gravis	☐	☐	☐
Unexplained generalized muscle weakness	☐	☐	☐	Organic brain disease	☐	☐	☐

Post-exertional malaise lasting more than 24 hours	☐	☐	☐	Rheumatological disorders e.g. rheumatoid arthritis, polymyositis	☐	☐	☐
Mild fever or chills	☐	☐	☐	Fibromyalgia Syndrome (FMS)	☐	☐	☐
Orthostatic intolerance or other autonomic manifestation	☐	☐	☐	Myofascial Pain Syndrome (MPS)	☐	☐	☐
Description of the main symptom complex as initially developing over a few hours to a few days	☐	☐	☐	Temporomandibular Joint Syndrome (TMJ),	☐	☐	☐
Prolonged (24 hours or greater) generalised fatigue from levels of exercise that would have been easily tolerated in the patient's premorbid state	☐	☐	☐	Chronic or sub-acute bacterial e.g. endocarditis, TB, Lyme disease	☐	☐	☐
Perceptual or sensory disturbances	☐	☐	☐	Irritable Bladder Syndrome	☐	☐	☐
Hypersensitivity to noise	☐	☐	☐	Irritable Bowel Syndrome	☐	☐	☐
Ataxia	☐	☐	☐	Raynaud's Phenomenon	☐	☐	☐
Mood disturbance	☐	☐	☐	Migraine	☐	☐	☐
Loss of thermostatic ability or other neuroendocrine manifestation	☐	☐	☐	Sicca Syndrome	☐	☐	☐
Intolerance of extremes of heat and cold	☐	☐	☐	Premenstrual Syndrome	☐	☐	☐
New sensitivities to food, medications and/or chemicals	☐	☐	☐	Multiple Chemical Sensitivity	☐	☐	☐
New onset of short term memory impairment	☐	☐	☐				
Confusion	☐	☐	☐				

Demographic details

1. Patient's age group 0-10 years ☐ 11-20 years☐ 21-30 years ☐ 31-40 years☐ 41-50 years☐ 51-60 years☐ 61-70 years ☐ >70 years ☐	**2. Does the patient have a degree or equivalent professional qualification?** Yes ☐ No☐ don't know☐ *Provide details if available……………………*
3. Marital status Married ☐ Single (never married) ☐ Widowed ☐ Single (separated) ☐ Divorced ☐	**4. Did education continue after the minimum school leaving age?** Yes ☐ No☐ don't know☐ *Provide details if available…*
5. Employment status Employed 36 hours a week or more ☐ Unemployed due to health ☐ Employed 18-36 hours a week ☐ Unemployed (jobseeker) ☐ Employed 9-18 hours a week ☐ Self employed ☐ Employed 0-9 hours a week ☐ Other (specify here)…………… Retired (specify last main job below) ☐ ……………………………………………….	**6. Race** -Asian/Asian British: Indian, Pakistani, Bangladeshi, Other Asian background☐ -Black/Black British: Caribbean, African, Any other black background☐ -White: White British, White Irish, Any other white background☐ Mixed background please state if known ☐…………………………….. Other: please state …………………………..
7. Sex Male ☐ Female ☐	**8.** What is your definitive diagnosis? …….....................

THANK YOU FOR YOUR HELP

Please return the completed proforma with the contact information sheet using the Freepost envelopes or to the following address: Tolu Osoba, Faculty of Applied Sciences, University of West England, Bristol BS16 1QY.

Appendix H Panel Invitation Letter

<Date>
<Name>
<Address>
<Address>

Dear <Name>

Invitation to Join an Expert Panel to support the Project: The Development of an Epidemiological Case-definition for Chronic Fatigue Syndrome (CFS/ME).

Because of your known expertise in the area, my supervisors and I would like to invite you to participate on an Expert Panel as noted above. This project has ethical approval from the South West Multi-centre Research Ethics Committee and forms the subject of my PhD research programme.

Aim of the Research Project
As you are probably aware, there are various clinical case-definitions of CFS/ME in existence. There is, however, no established epidemiological case-definition for CFS/ME. The lack of an epidemiological definition for CFS/ME has posed the greatest obstacle to CFS/ME research. Therefore, the aim of this project is to develop an epidemiological case-definition for CFS/ME that would enable comparison across studies, facilitate documentation of the public health burden of the condition in the UK, and assist in the planning and delivery of quality health services for CFS/ME patients.
The data for the project have been provided by General Practitioners in the UK who have completed a proforma of CFS/ME symptoms derived from well-known research definitions.
This project is sponsored by the Faculty of Applied Sciences, at the University of the West of England in Bristol.

What will you be asked to do?
The next stage of the project requires the input of an Expert Panel. The Expert Panel will be composed of 5 individuals with special interests, professional expertise and ability to contribute to CFS/ME research. You were identified as having individual expertise relative to CFS/ME as a member of the Chief Medical Officer's 2002 CFS/ME Working group.
A modified delphi technique will be employed at this stage. The focus of Panellists will be to assign cases to disease and non-disease groups using the data collected during the course of the project. An example of the Panel proforma used is enclosed. The assignment of cases will involve three rounds of reviews. During the first round, Panellists will rank cases into categories. Feedback on the results will be provided in the second round and Panellists will be asked to re-rank cases with disagreement. At the third round, Panellists will meet to discuss cases where disagreement has become apparent.
Overall, the time commitment is estimated to be approximately 2 non-consecutive days. This is inclusive of the first two rounds reviews that will take place in October and November 2005 and of a half day consensus meeting in London in January 2006.

What benefits will I receive?
We value your expertise and hope to have your help as a Panellist for this vital work. Your contribution will be acknowledged in the thesis and external publications.
In addition, we are offering an honorarium of £200 as well as covering other expenses associated with your involvement as a member of the Expert Panel. We realise this is far below your normal fee and hope you will consider this invitation because of the importance of this work. A schedule and further study details will be sent to Panellists upon receipt of the acceptance slip below.

Do you have any questions?
If there is any issue relating to this project that serves as a barrier to your contribution as a Panellist, please let us know and we will try to work out other arrangements. We welcome your suggestions on other individuals who might be interested in becoming Panellists. You can contact Tolu Osoba on 07762715268 or by email at tolulope2.osoba@uwe.ac.uk

We will call you shortly to answer any questions you might have and to see if you will be able to join the Panel. If you accept, we will also ask whether you are available for selected dates for the meeting in January 2006 that is most convenient for you.
In any event, please would you confirm your acceptance or otherwise of this invitation no later than 1 August 2005. A tear-off slip and pre-paid envelope are provided for your convenience.
We look forward to hearing from you.

Thank you.

Yours sincerely,

Tolu Osoba
Postgraduate Research Student
Faculty of Applied Sciences
University of the West of England

Dr Selena Gray
Reader in Public Health
Faculty of Health and Social Care
University of the West of England

Professor John Duffield
Associate Dean (Resources)
Faculty of Applied Sciences
University of the West of England

Enc: 1 copy Ethics approval letter
1 copy proforma

Strike out the option which does not apply
(a) I accept the invitation to be an Expert Panellist on the CFS/ME project.
(b) Thank you for the invitation, but I do not wish to be an Expert Panellist on the CFS/ME project.

Name: ______________________ Signed: ______________________

Appendix I Panel Thank You Letter

<Date>
<Name>
<Address>
<Address>

Dear <Name>

We are honoured to have your help on the expert panel for the study titled: the development of an epidemiological case-definition for Chronic Fatigue Syndrome.
The following lines are intended to give you an idea of the conduct of the 3-stage panel review and to provide some practical guidance for your involvement with the study. We shall start sending the material to all panellists late September and hope to have everything dispatched by early October. You will receive all essential material in hard copy. This will compose: a maximum of 35 proformas completed by GPs, an outline of the review process, ranking sheets and reply paid envelopes for the return of assessed material.

Please find enclosed an information sheet titled "proposed schedule for the Expert Panel" and a sample of the ranking sheet which presents the criteria to be used in the assessment and the rating scale with descriptions. For the conduct of this exercise, it is vital that panellists interpret the rating scale in a nearly similar manner. There will be no exact directions for the panellist's working methods; therefore the first two rounds of reviews should take place at a time of your own choosing during the following periods:

First round
Monday, October 17 2005 through Saturday, November 5 2005.

Second round
Monday, November 14 2005 through Monday, December 5 2005.

Third round*
Monday January 9 2006 through Monday, January 23 2006.
*For the third round of reviews please confirm which of these days are convenient for you to meet in January. The meeting should take no longer than 2 hours and will be held at a central location with good transport links. The current dates selected are the 11th or the 18th of January 2006. If neither of the dates is convenient for you, please provide us with alternate dates within the stipulated period. Details of the meeting venue including maps and directions will be provided nearer the time.

Please note that in the absence of disagreement on group classifications, the third round of reviews will not take place. As mentioned in the invitation letter, the panellists will be paid a fee of £200 and reimbursed for all expenses associated with their involvement with the study. Please ensure that you document all related expenses and retain receipts where possible.
Should you require anything further, please contact Tolu Osoba on 07762715268 or email tolulope2.osoba@uwe.ac.uk

We are happy you can join us and look forward to your contributions to this important study of CFS/ME.
Thank you for accepting the invitation.

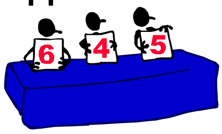
Yours sincerely,

……………………………………………..
Tolu Osoba
PhD student
Faculty of Applied Sciences
University of the West of England

…….…………………………………….
Professor Selena Gray
Reader in Public Health
Faculty of Health and Social Care
University of the West of England

……………………………………………
Professor John Duffield
Associate Dean (Resources)
Faculty of Applied Sciences
University of the West of England

Appendix J Expert Panel Information Sheet



Introduction

The aim of this study is to develop an epidemiological case-definition for Chronic Fatigue Syndrome (CFS/ME).

Chronic Fatigue Syndrome or CFS/ME has been defined as ‘a debilitating and complex disorder characterised by profound fatigue that is not improved by bed rest and that may be worsened by physical or mental activity[3]. It has also been associated with several symptoms which include fevers, pharyngitis, musculoskeletal pain, sleep disturbances, impaired concentration, depression and headaches. There is no diagnostic test or pathognomonic medical characteristic that can validate its diagnosis.

There are many controversies surrounding CFS/ME ranging from the choice of name to methods employed in the research and management of the condition.

There is currently no ‘gold standard’ epidemiological case-definition for CFS/ME. The lack of an epidemiological case-definition for CFS/ME has resulted in the use of clinical and non-standardised exclusion criteria in public health related research on CFS/ME. This has created wide ranging estimates of the prevalence of the condition and in most cases the true burden of the condition in the general population has been underestimated.

The current research

A checklist of symptom criteria was developed from the current case-definitions for CFS/ME. This was designed as a proforma, to be inclusive of all symptoms associated with CFS/ME as identified in the literature as well as important exclusive criteria to aid in distinguishing between CFS/ME and other diseases that mimic symptoms experienced by CFS/ME patients.

General Practitioners in the UK were asked to complete the proformas for all current cases of unexplained chronic fatigue of at least six months duration. The ‘six months duration of unexplained chronic fatigue’ fulfilled one of the requirements of the 1988 and 1994 CDC, Australia, Oxford and Canadian definitions of CFS/ME.

The next stage of the study involves the input of an expert panel in identifying possible cases of CFS/ME due to the lack of a gold standard epidemiological case-definition.

---

[3] CFIDS Association of America, 2001

Task of the Expert Panel

The focus of the Expert Panel is to independently evaluate the proformas and assign cases to disease (possible cases of CFS/ME) or non-disease groups (unlikely cases of CFS/ME).

(i) The method

The work with the Panellists will use a modified-delphi technique. The delphi technique is a research approach used to gain consensus through a series of rounds of questionnaire-type surveys, usually two or three, where information and results are fed back to panel members between each round. Each Panellist will work independently. There will be two rounds of review and a consensus meeting to resolve issues around disagreement.

(ii) First round- Monday, October 17 2005 through Saturday, November 5 2005.

Panellists will be sent a pack containing the proformas and further details of the process. They will be asked to complete and return a confirmation slip or contacted by phone a week later to ensure that they have received the pack and to explore possible problems.

In this round, Panellists will be asked to rate cases as 'possible' or 'unlikely' cases of CFS/ME. In addition they will be asked to indicate their level of confidence of their choice of group on a 5-point scale as shown below.

Point Quantitative Scale for Confidence Levels[4]

5 : Very High Confidence

4 : High Confidence

3 : Medium Confidence

2 : Low Confidence

1 : Very Low Confidence

The end goal of the entire review process is to identify criteria within disease groups (possible cases) that assist in distinguishing between individuals with CFS/ME from those with other forms of chronic fatigue.

Once all Panellists have completed the round, the responses will be collated. The results will then be shared with the group.

(iii) Second round

Monday, November 14 2005 through Monday, December 5 2005.

---

[4] http://www.deh.gov.au/biodiversity/publications/nbccap-consultation/appendix-f.html

Feedback from first round review will be provided during the second round. Each Panellist will receive a copy of all the first round ratings, together with his/her own specific ratings and a summary of the average ratings. The assumption is that, provided with this feedback, a rater will begin to make decisions or ratings more consistent with the group norm.[5] Cases with disagreement will be highlighted.

The second round will follow the same pattern as the first round. Panellists will be asked to re-rate all the cases for the purpose of testing reliability measures for cases without disagreement i.e. cases with agreement from the first round. The extent of agreement between the Panellists will be determined from the confidence-level data and assessed by statistical measures.

At the end of the allotted time frame, the responses will be collated. All responses will be made anonymous. Only the researcher will be able to link a response to a particular Panellist. In reviewing the tallies for each round, the researcher may contact Panellists to get clarification about a response. If cases with disagreement still exist, these will be identified and sent to Panellists ahead of the consensus meeting in January.

(iv) Third round

Monday January 9 2006 through Monday, January 23 2006.

The panel will meet to discuss the ratings focusing on areas of disagreement.

Each Panellist will receive a copy of the results of all the second round ratings, together with his/her own specific ratings. Panellists will be expected to reach a consensus.

[5] http://ourworld.compuserve.com/homepages/jsuebersax/cont.htm

Simple flowchart outlining the process

Invitation to Expert Panellists (N=3) &
confirmation of acceptance to join the panel

(July-August 2005)

Round 1: Panellists receive proformas (30 - 40 forms per rater) and instructions.

Rating of cases as 'possible' or 'unlikely'.

Confidence level indicated

October 17 2005 - November 5 2005

Round 2: Feedback of first round results.

Re-rating of all cases
Highlighting areas of disagreement from the first round.

November 14 2005 - December 5 2005

Round 3: Consensus meeting

January 9 2006 - January 23 2006

Appendix K Panellists' Assessment Sheet

Expert Panel Assessment Sheet
Review Round 1: October 17 2005 - November 5 2005

1. Based on your expert judgment of the information provided in the proforma please indicate the outcome of your assessment of the case by ticking one of the options provided below.

Disease group (Possible case of CFS/ME) ✔	☐
Non-disease group (unlikely case of CFS/ME) ✖	☐

2. How confident are you of your assessment? Please indicate your confidence level by ticking one of the boxes below.

Point Quantitative Scale for Confidence Levels		**Tick box**
5	Very High Confidence	☐
4	High Confidence	☐
3	Medium Confidence	☐
2	Low Confidence	☐
1	Very Low Confidence	☐

3. Please give your initial and the ID number of the proforma assessed below.

Panellist's initials ………………… Proforma ID ……………….

Please return your completed forms latest by the 7th of November, 2005.

Thank you for your help.

Appendix L Conversion table for combining reviewers' case assignment and confidence ratings

Table 69 Case assignment conversion table

Case assignment	Confidence level at which the choice was made	Resultant score-
1 (CFS/ME)	5 (very high)	9
1 (CFS/ME)	4 (high)	8
1 (CFS/ME)	3 (medium)	7
1 (CFS/ME)	2 (low)	6
1 (CFS/ME)	1 (very low)	5
0 (NON-CFS/ME)	1 (very low)	4
0 (NON-CFS/ME)	2 (low)	3
0 (NON-CFS/ME)	3 (medium)	2
0 (NON-CFS/ME)	4 (high)	1
0 (NON-CFS/ME)	5 (very high)	0

Appendix M Summary measures of questions and medical explanations of symptoms in light of current research. [6,7]

(Current WHO International Classification of Disease codes (ICD 10) are given where available).

Definitions

- *Signs- these are objective findings that can be observed and described by a health care professional. The information is usually found in the physical exam or physical findings section of a patient's medical record.*[8]

- *Symptoms- these are subjective evidence of a disease or condition as perceived and reported by the patients and include reported changes from normal function and sensation. The information is usually found in the medical history section of the patient's medical record.*

1. **Fatigue symptoms** (ICD 10- F48.0, fatigue is classified under neurotic, stress-related and somatoform disorders as neurasthenia):

a. Debilitating fatigue not relieved by bed rest
b. Chronic persisting or relapsing fatigue
c. Severe disabling fatigue affecting physical and mental functioning
d. Post-exertional fatigue or malaise lasting more than 24 hours
e. Mental fatigue

According to the ICD 10, two main types occur, with substantial overlap. In one type, the main feature is a complaint of increased fatigue after mental effort, often associated with some decrease in occupational performance or coping efficiency in daily tasks. The mental fatigability is typically described as an unpleasant intrusion of distracting associations or recollections, difficulty in concentrating, and generally inefficient thinking. In the other type, the emphasis is on feelings of bodily or physical weakness and exhaustion after only minimal effort, accompanied by a feeling of muscular aches and pains and inability to relax.

2. **Infection at onset or presentation corroborated by laboratory evidence**
3. **Immune signs and symptoms**

a. New sensitivities to food, medications and/or chemicals
b. Sore throat
c. Painful cervical or axillary lymph nodes
d. Swollen lymph nodes
e. Mild fever or chills

---

[6] The Merck Manual of Medical Information, Second Edition: Mark H. Beers - April 2003.

[7] http://www.medicinenet.com/script/main/hp.asp accessed 20th September 2006

[8] http://www.cdc.gov/niosh/topics accessed 10th October 2006.

4. **6 months minimum duration of fatigue or illness**

5. **Description of the main symptom complex as initially developing over a few hours to a few days**

6. **Functional impairment and disruption of normal activity**

a. Substantial functional impairment

b. 50% decrease in activity compared to premorbid levels

c. Significant disruption of usual activities

d. Functional impairment that can be described as disabling

7. **Musculoskeletal symptoms**

a. Muscle discomfort/Myalgia (ICD10- M79 classified under soft tissue disorders: pain in a muscle or muscles): Myalgia is a term used to describe muscle pain, which is generally accompanied by malaise.

b. Migratory arthralgia without joint swelling or redness (ICD10- M25.5 classified under disorders affecting predominantly peripheral (limb) joints): Arthralgia is the symptom of painful joints.

c. Muscle pain, multi-joint pain without swelling or redness

d. Unexplained generalized muscle weakness:

8. **Visual disturbances**

a. Photophobia (ICD10- H53.1 classified under subjective visual disturbances): abnormal visual intolerance of light.

b. Transient visual scotomata (ICD10- H53.4, H53.1 classified under subjective visual disturbances): an area of lost or depressed vision within the visual field, surrounded by an area of less depressed or of normal vision.

9. **Psychiatric and mental symptoms**

a. Anxiety disorder (ICD10- F41 classified under neurotic, stress-related and somatoform disorders): Anxiety disorders involve a state of distressing chronic but fluctuating nervousness that is inappropriately severe for the person's circumstances.

b. Mood disturbance (ICD10- F30 classified under affective disorders): These are disorders in which the fundamental disturbance is a change in affect or mood to depression (with or without associated anxiety) or to elation. The mood change is usually accompanied by a change in the overall level of activity; most of the other symptoms are either secondary to, or easily understood in the context of, the change in mood and activity. Most of these disorders tend to be recurrent and the onset of individual episodes can often be related to stressful events or situations.

c. Excessive irritability: A primary symptom of mood (affective), schizophrenic and delusional disorders.

d. Depression (ICD10- F32 classified under affective disorders): It is a mental state of depressed mood characterized by feelings of sadness, despair, and discouragement. In typical mild, moderate, or severe depressive episodes, the patient suffers from lowering of mood, reduction of energy, and decrease in activity. Capacity for enjoyment, interest, and concentration is reduced, and marked tiredness after even minimum effort is common. Sleep is usually disturbed and appetite diminished. Self-esteem and self-confidence are almost always reduced and, even in the mild form, some ideas of guilt or worthlessness are often present.

10. Neurological and cognitive symptoms

Neurological

a. Ataxia (ICD10- R27.0 classified under symptoms and signs involving the nervous and musculoskeletal systems): failure of muscular coordination; irregularity of muscular action.

b. Sleep disturbance (hypersomnia or insomnia or unrefreshing sleep): ICD 10- F51 classified under non-organic sleep disorders. This category includes only those sleep disorders in which emotional causes are considered to be a primary factor, and which are not due to identifiable physical disorders.

c. Generalised headaches (of a type, severity, or pattern that is different from headaches the patient may have had in the premorbid state)

d. Hypersensitivity to noise, perceptual or sensory disturbances.

Cognitive

e. Confusion (ICD10- F05 classified under delirium, not induced by alcohol and other psychoactive substances): This is the inability to process information normally. Delirium is a term often used to describe any type of confusion. It is a sudden, fluctuating, and usually reversible cognitive disorder characterized by disorientation, the inability to pay attention, the inability to think clearly, and a change in the level of consciousness.

f. Forgetfulness: (see e. above)

g. Difficulty thinking: (see e. above)

h. Inability to concentrate: (see e. above)

i. New onset of short term memory impairment: (see e. above)

11. Orthostatic intolerance or autonomic manifestation: Orthostatic intolerance is the development of symptoms during upright standing relieved by recumbence. It includes neurally mediated hypotension, delayed orthostatic hypotension, and postural orthostatic tachycardia

syndrome, all of which are considered forms of dysautonomia.[9] Other autonomic manifestations include light-headedness; extreme pallor; nausea and irritable bowel syndrome; urinary frequency and bladder dysfunction; palpitations with or without cardiac arrhythmias; exertional dyspnea.

12. Loss of thermostatic ability or other neuroendocrine manifestation: Includes intolerance of extremes of heat and cold, subnormal body temperature and marked diurnal fluctuation, sweating episodes, recurrent feelings of feverishness and cold extremities.

13. Comorbid and overlapping conditions

a. Irritable Bowel Syndrome (ICD K58-classified under diseases of the intestine): It is a disorder of motility of the entire digestive tract that causes abdominal pain, constipation, or diarrhoea.

b. Multiple Chemical Sensitivity (ICD10 T78.4- classified under injury, poisoning and certain other consequences of external causes- unspecified effects of external causes): Multiple Chemical Sensitivity Syndrome is a disorder that appears to be triggered by low-level exposure to multiple chemical substances commonly found in the environment. Symptoms include a rapid heart rate, chest pain, sweating, shortness of breath, fatigue, flushing, dizziness, nausea, choking, trembling, numbness, coughing, hoarseness, and difficulty concentrating

c. Fibromyalgia (ICD10- M79.7 classified as a soft tissue disorder): Fibromyalgia is characterised by achy pain and stiffness in soft tissues, including muscles, tendons, and ligaments. The pain is either diffuse or has multiple trigger points). The term fibromyalgia is used to describe several related disorders including generalised fibromyalgia, primary fibromyalgia syndrome, secondary fibromyalgia syndrome, localized fibromyalgia, and myofascial pain syndrome, each having different connotations.

d. Raynaud's Phenomenon: (ICD10 I73.0- classified under diseases of arteries, arterioles and capillaries): is a condition involving intermittent bilateral ischemia of the fingers, toes, and sometimes ears and nose, with severe pallor and often paresthesias and pain, usually brought on by cold or emotional stimuli and relieved by heat; it is usually due to an underlying disease or anatomical abnormality.

e. Premenstrual Syndrome (ICD10 N94.3- classified under pain and other conditions associated with female genital organs and menstrual cycle): Premenstrual syndrome (PMS) is a group of physical and psychologic symptoms that occur before a menstrual period begins.

---

[9] Stewart, J. M., & Erickson, L.C., (2002). Orthostatic intolerance: an overview. In Alejos, J. C., Konop, R., Chin, A. J., Herzberg, G., Neish, S. (Eds.). emedicine Journal, 3, (1). http://www.emedicine.com/ped/topic2860.htm accessed 19092006

f. Migraine (ICD10 G43- classified under diseases of the nervous system and episodic and paroxysmal disorders): In a migraine, throbbing pain is typically felt on one side of the head. The pain may be moderate but is often severe and incapacitating. Physical activity, light, sounds, or smells may make the headache worse. The headache is often accompanied by nausea, sometimes with vomiting. A migraine attack often involves more than a headache. It may include a prodrome, an aura, and a postdrome.

g. Sicca Syndrome (ICD 10 M35.0- classified under systemic connective tissue disorders and diseases of the musculoskeletal system and connective tissue): is characterized by excessive dryness of the eyes, mouth, and other mucous membranes.

h. Irritable Bladder Syndrome: is a syndrome characterized by symptoms of urinary urgency with or without urgency urinary incontinence (UUI), usually with increased frequency of contraction and nocturia.

i. Myofascial Pain Syndrome: Myofascial pain is a chronic condition that affects the fascia (connective tissue that covers the muscles). Myofascial pain syndrome may involve either a single muscle or a muscle group. In some cases, the area where a person experiences the pain may not be where the myofascial pain generator is located. Experts believe that the actual site of the injury or the strain prompts the development of a trigger point that, in turn, causes pain in other areas. This situation is known as referred pain.

j. Temporomandibular Joint Syndrome (ICD 10 K07.6- classified under dentofacial anomalies): Disorder of the temporo-mandibular joint (TMJ) causing pain usually in front of the ear. Pain in the TMJ can be due to trauma (such as a blow to the face), inflammatory or degenerative arthritis, or by the mandible being pushed back towards the ears whenever the patient chews or swallows. Sometimes, muscles around the TMJ used for chewing can go into spasm, causing head and neck pain and difficulty opening the mouth normally.

k. Interstitial Cystitis (ICD 10 N30.1- classified under diseases of the urinary system): is a condition that results in recurring discomfort or pain in the bladder and the surrounding pelvic region on bladder filling and at the end of micturition. Symptoms vary and may include an urgent need to urinate (urgency), a frequent need to urinate (frequency), or a combination of these symptoms.

l. Hashimoto's Disease (ICD 10 E06.3- classified under disorders of the thyroid): It is the most common type of thyroiditis and the most common cause of hypothyroidism. For unknown reasons, the body turns against itself (an autoimmune reaction); the thyroid is invaded by white blood cells, and antibodies are created that attack the thyroid gland.

m. Hyperventilation syndrome (ICD 10 R06.4- classified under disorders of breathing): Hyperventilation syndrome causes people to feel that they cannot get enough air, and they breathe heavily and rapidly. This condition is commonly caused by anxiety rather than a physical problem. The symptoms result from changes in the blood gas levels (mostly from a lowering of the

carbon dioxide level) caused by the over breathing. There may be a change in consciousness usually described as a feeling that events occurring around them are far away, and experience of a tingling feeling in the hands and feet and around the mouth.

14. Other Diseases/ exclusions

a. Anaemia
b. Addison's disease
c. Cushing's Syndrome
d. Hyperthyroidism
e. Hypothyroidism
f. Diabetes mellitus
g. Cancer
h. Upper airway resistance syndrome
i. Obstructive or central sleep apnea
j. Iron overload syndrome
k. Fungal disease e.g. histoplasmosis or coccidioidomycosis
l. Parasitic disease e.g. toxoplasmosis or other helminthic infestation
m. Other infectious diseases e.g. HIV infection, chronic hepatitis
n. Psychosis
o. Vitamin B12 deficiency
p. Depressive disorder including endogenous depression
q. Bipolar disorder
r. Schizophrenia
s. Substance abuse
t. Melancholic (severe, major) or psychotic depression
u. Eating disorder
v. Dementia
w. Delusional disorders
x. Neurological disorders e.g. multiple sclerosis (MS), Parkinsonism, Myasthenia gravis
y. Organic brain disease
z. Rheumatological disorders e.g. rheumatoid arthritis, polymyositis
aa. Chronic or sub acute bacterial e.g. endocarditis, TB, Lyme disease

Appendix N Prevalence of chronic fatigue symptoms and disorders by classification cut-off score

Table 70 Cross tabulation of cases (CFS/ME group) and controls (Non CFS/ME group)

		classification cut-off score 5 or>				classification cut-off score 6 or>				classification cut-off score 7 or>				classification cut-off score 8 or>			
ORIGINAL DATASET		Non CFS/ME	CFS/ME	Total	P-value	Non CFS/ME	CFS/ME	Total	P-value	Non CFS/ME	CFS/ME	Total	P-value	Non CFS/ME	CFS/ME	Total	P-value
Debilitating fatigue not relieved by bed rest	no	6	16	22	0.523	6	16	22	0.773	10	12	22	0.75	16	6	22	0.282
	yes	26	97	123		37	85	122		51	71	122		74	48	122	
	Total	32	113	145		43	101	144		61	83	144		90	54	144	
Chronic persisting or relapsing fatigue	yes	35	118	153	.(a)	47	105	152	.(a)	68	84	152	.(a)	98	54	152	.(a)
	Total	35	118	153		47	105	152		68	84	152		98	54	152	
Severe disabling fatigue affecting physical and mental functioning	no	8	6	14	0.001	9	5	14	0.003	11	3	14	0.005	12	2	14	0.07
	yes	24	111	135		35	99	134		53	81	134		82	52	134	
	Total	32	117	149		44	104	148		64	84	148		94	54	148	
Infection at onset or presentation corroborated by laboratory evidence	no	24	64	88	0.084	31	57	88	0.059	44	44	88	0.056	59	29	88	0.071
	yes	5	33	38		7	31	38		12	26	38		19	19	38	
	Total	29	97	126		38	88	126		56	70	126		78	48	126	
Substantial functional impairment	no	11	16	27	0.016	13	14	27	0.035	14	13	27	0.388	21	6	27	0.105
	yes	24	101	125		34	90	124		53	71	124		76	48	124	
	Total	35	117	152		47	104	151		67	84	151		97	54	151	
50% decrease in activity	no	9	7	16	0	9	7	16	0.003	11	5	16	0.016	15	1	16	0.005
	yes	18	106	124		27	96	123		46	77	123		71	52	123	
	Total	27	113	140		36	103	139		57	82	139		86	53	139	
Significant disruption of usual activities	no	1	4	5	0.941	2	3	5	0.602	2	3	5	0.868	3	2	5	0.859
	yes	31	114	145		42	102	144		63	81	144		92	52	144	
	Total	32	118	150		44	105	149		65	84	149		95	54	149	
Functional impairment that can be described as disabling	no	9	15	24	0.066	10	14	24	0.224	12	12	24	0.594	18	6	24	0.258

	yes	26	102	128		37	90	127		56	71	127		80	47	127	
	Total	35	117	152		47	104	151		68	83	151		98	53	151	
Presence of cognitive or neuropsychiatric symptoms	no	17	44	61	0.393	20	41	61	0.986	31	30	61	0.266	44	17	61	0.164
	yes	18	65	83		27	55	82		34	48	82		50	32	82	
	Total	35	109	144		47	96	143		65	78	143		94	49	143	
Mental fatigue	no	4	12	16	0.826	4	12	16	0.619	6	10	16	0.508	11	5	16	0.73
	yes	30	103	133		41	91	132		61	71	132		85	47	132	
	Total	34	115	149		45	103	148		67	81	148		96	52	148	
Photophobia	no	30	81	111	0.157	38	72	110	0.232	53	57	110	0.241	71	39	110	0.468
	yes	3	20	23		5	18	23		8	15	23		13	10	23	
	Total	33	101	134		43	90	133		61	72	133		84	49	133	
Transient visual scotomata	no	31	87	118	0.387	41	76	117	0.563	55	62	117	0.602	76	41	117	0.394
	yes	1	7	8		2	6	8		3	5	8		4	4	8	
	Total	32	94	126		43	82	125		58	67	125		80	45	125	
Depression	no	10	43	53	0.26	12	41	53	0.051	16	37	53	0.009	26	27	53	0.007
	yes	25	67	92		35	56	91		48	43	91		65	26	91	
	Total	35	110	145		47	97	144		64	80	144		91	53	144	
Forgetfulness	no	14	30	44	0.197	18	25	43	0.173	24	19	43	0.057	33	10	43	0.022
	yes	18	66	84		25	59	84		32	52	84		47	37	84	
	Total	32	96	128		43	84	127		56	71	127		80	47	127	
Excessive irritability	no	21	42	63	0.061	27	35	62	0.071	33	29	62	0.215	40	22	62	0.896
	yes	12	52	64		18	46	64		27	37	64		42	22	64	
	Total	33	94	127		45	81	126		60	66	126		82	44	126	
Difficulty thinking	no	14	22	36	0.017	15	20	35	0.132	21	14	35	0.031	27	8	35	0.055
	yes	19	81	100		29	71	100		39	61	100		59	41	100	
	Total	33	103	136		44	91	135		60	75	135		86	49	135	
Inability to concentrate	no	8	16	24	0.216	9	15	24	0.498	12	12	24	0.559	18	6	24	0.191
	yes	25	91	116		35	80	115		50	65	115		70	45	115	
	Total	33	107	140		44	95	139		62	77	139		88	51	139	
Substantial impairment in short-term memory or concentration	no	16	36	52	0.105	18	33	51	0.359	26	25	51	0.114	38	13	51	0.013
	yes	14	62	76		21	55	76		28	48	76		40	36	76	
	Total	30	98	128		39	88	127		54	73	127		78	49	127	

Sore throat	no	26	69	95	0.123	34	61	95	0.042	46	49	95	0.11	62	33	95	0.216
	yes	6	34	40		7	32	39		13	26	39		21	18	39	
	Total	32	103	135		41	93	134		59	75	134		83	51	134	
Painful cervical or axillary lymph nodes	no	31	76	107	0.057	40	66	106	0.024	53	53	106	0.058	72	34	106	0.024
	yes	3	24	27		4	23	27		8	19	27		12	15	27	
	Total	34	100	134		44	89	133		61	72	133		84	49	133	
Swollen lymph nodes	no	32	80	112	0.025	42	69	111	0.015	55	56	111	0.014	76	35	111	0.004
	yes	1	19	20		2	18	20		4	16	20		7	13	20	
	Total	33	99	132		44	87	131		59	72	131		83	48	131	
Muscle discomfort	no	18	21	39	0	22	17	39	0	28	11	39	0	35	4	39	0
	yes	16	92	108		24	83	107		38	69	107		59	48	107	
	Total	34	113	147		46	100	146		66	80	146		94	52	146	
Myalgia	no	14	20	34	0.006	17	17	34	0.009	22	12	34	0.006	29	5	34	0.002
	yes	20	89	109		28	80	108		41	67	108		60	48	108	
	Total	34	109	143		45	97	142		63	79	142		89	53	142	
Migratory arthralgia without joint swelling or redness	no	23	58	81	0.094	30	50	80	0.046	38	42	80	0.171	56	24	80	0.018
	yes	9	47	56		12	44	56		20	36	56		28	28	56	
	Total	32	105	137		42	94	136		58	78	136		84	52	136	
Multi-joint pain without swelling or redness	no	25	61	86	0.04	33	52	85	0.02	42	43	85	0.067	58	27	85	0.045
	yes	7	44	51		10	41	51		17	34	51		26	25	51	
	Total	32	105	137		43	93	136		59	77	136		84	52	136	
Generalised headaches (different from headaches the patient may have had in the premorbid state)	no	20	49	69	0.097	27	41	68	0.052	38	30	68	0.006	50	18	68	0.007
	yes	12	58	70		17	53	70		23	47	70		36	34	70	
	Total	32	107	139		44	94	138		61	77	138		86	52	138	
Sleep disturbance (hypersomnia or insomnia or unrefreshing sleep)	no	6	16	22	0.606	8	14	22	0.605	12	10	22	0.24	15	7	22	0.555
	yes	26	91	117		36	81	117		48	69	117		72	45	117	
	Total	32	107	139		44	95	139		60	79	139		87	52	139	
Anaemia	no	30	112	142	0.041	41	100	141	0.139	60	81	141	0.097	89	52	141	0.441
	yes	3	2	5		3	2	5		4	1	5		4	1	5	
	Total	33	114	147		44	102	146		64	82	146		93	53	146	

Addison's disease	no	35	113	148	.(a)	47	100	147	.(a)	66	81	147	.(a)	95	52	147	.(a)
	Total	35	113	148		47	100	147		66	81	147		95	52	147	
Cushing's Syndrome	no	35	114	149	.(a)	47	101	148	.(a)	66	82	148	.(a)	95	53	148	.(a)
	Total	35	114	149		47	101	148		66	82	148		95	53	148	
Hyperthyroidism	no	33	115	148	.(a)	45	102	147	.(a)	65	82	147	.(a)	95	52	147	.(a)
	Total	33	115	148		45	102	147		65	82	147		95	52	147	
Hypothyroidism	no	27	108	135	0.05	39	95	134	0.287	56	78	134	0.107	82	52	134	0.019
	yes	6	8	14		6	8	14		9	5	14		13	1	14	
	Total	33	116	149		45	103	148		65	83	148		95	53	148	
Hashimoto's Disease	no	33	112	145	0.364	45	99	144	0.571	64	80	144	0.117	91	53	144	0.282
	yes	1	1	2		1	1	2		2	0	2		2	0	2	
	Total	34	113	147		46	100	146		66	80	146		93	53	146	
Diabetes mellitus	no	34	117	151	.(a)	46	104	150	.(a)	66	84	150	.(a)	96	54	150	.(a)
	Total	34	117	151		46	104	150		66	84	150		96	54	150	
Cancer	no	33	116	149	0.07	45	103	148	0.179	65	83	148	0.432	95	53	148	0.929
	yes	2	1	3		2	1	3		2	1	3		2	1	3	
	Total	35	117	152		47	104	151		67	84	151		97	54	151	
Upper airway resistance syndrome	no	33	113	146	0.067	45	100	145	0.139	65	80	145	0.269	92	53	145	0.449
	yes	1	0	1		1	0	1		1	0	1		1	0	1	
	Total	34	113	147		46	100	146		66	80	146		93	53	146	
Obstructive or central sleep apnea	no	31	111	142	0.598	42	100	142	0.518	62	80	142	0.38	91	51	142	0.184
	yes	0	1	1		0	1	1		0	1	1		0	1	1	
	Total	31	112	143		42	101	143		62	81	143		91	52	143	
Iron overload syndrome	no	34	113	147	.(a)	46	100	146	.(a)	65	81	146	.(a)	93	53	146	.(a)
	Total	34	113	147		46	100	146		65	81	146		93	53	146	
Hyperventilation syndrome	no	32	109	141	0.602	41	99	140	0.119	60	80	140	0.457	87	53	140	0.207
	yes	1	6	7		4	3	7		4	3	7		6	1	7	
	Total	33	115	148		45	102	147		64	83	147		93	54	147	
Interstitial Cystitis	no	33	111	144	0.922	44	99	143	0.413	63	80	143	0.813	91	52	143	0.577
	yes	1	3	4		2	2	4		2	2	4		2	2	4	
	Total	34	114	148		46	101	147		65	82	147		93	54	147	
Fungal disease e.g. histoplasmosis or coccidioidomycosis	no	34	116	150	.(a)	46	103	149	.(a)	66	83	149	.(a)	96	53	149	.(a)

	Total	34	116	150		46	103	149		66	83	149		96	53	149	
Parasitic disease e.g. toxoplasmosis or other helminthic infestation	no	33	116	149	0.064	45	103	148	0.133	65	83	148	0.261	95	53	148	0.456
	yes	1	0	1		1	0	1		1	0	1		1	0	1	
	Total	34	116	150		46	103	149		66	83	149		96	53	149	
Other infectious diseases e.g. HIV infection, chronic hepatitis	no	33	113	146	0.36	45	100	145	0.566	65	80	145	0.884	94	51	145	0.299
	yes	1	1	2		1	1	2		1	1	2		2	0	2	
	Total	34	114	148		46	101	147		66	81	147		96	51	147	
Psychosis	no	33	115	148	0.353	45	102	147	0.556	64	83	147	0.855	94	53	147	0.684
	yes	1	1	2		1	1	2		1	1	2		1	1	2	
	Total	34	116	150		46	103	149		65	84	149		95	54	149	
Vitamin B12 deficiency	no	31	111	142	0.184	43	98	141	0.406	62	79	141	0.219	90	51	141	0.646
	yes	2	2	4		2	2	4		3	1	4		3	1	4	
	Total	33	113	146		45	100	145		65	80	145		93	52	145	
Anxiety disorder	no	19	97	116	0	26	89	115	0	43	72	115	0.003	66	49	115	0.004
	yes	15	18	33		20	13	33		22	11	33		28	5	33	
	Total	34	115	149		46	102	148		65	83	148		94	54	148	
Depressive disorder including endogenous depression	no	18	83	101	0.029	24	76	100	0.005	38	62	100	0.027	56	44	100	0.003
	yes	16	31	47		22	25	47		27	20	47		38	9	47	
	Total	34	114	148		46	101	147		65	82	147		94	53	147	
Bipolar disorder	no	32	116	148	0.009	44	103	147	0.033	64	83	147	0.11	93	54	147	0.283
	yes	2	0	2		2	0	2		2	0	2		2	0	2	
	Total	34	116	150		46	103	149		66	83	149		95	54	149	
Schizophrenia	no	35	117	152	.(a)	47	104	151	.(a)	67	84	151	.(a)	97	54	151	.(a)
	Total	35	117	152		47	104	151		67	84	151		97	54	151	
Substance abuse	no	32	115	147	0.009	44	102	146	0.034	64	82	146	0.112	93	53	146	0.288
	yes	2	0	2		2	0	2		2	0	2		2	0	2	
	Total	34	115	149		46	102	148		66	82	148		95	53	148	
Melancholic (severe, major) or psychotic depression	no	33	112	145	0.444	43	101	144	0.538	62	82	144	0.107	91	53	144	0.282
	yes	0	2	2		1	1	2		2	0	2		2	0	2	
	Total	33	114	147		44	102	146		64	82	146		93	53	146	

Eating disorder	no	32	112	144	0.206	43	100	143	0.132	62	81	143	0.145	90	53	143	0.22
	yes	3	4	7		4	3	7		5	2	7		6	1	7	
	Total	35	116	151		47	103	150		67	83	150		96	54	150	
Dementia	no	35	116	151	.(a)	47	103	150	.(a)	67	83	150	.(a)	96	54	150	.(a)
	Total	35	116	151		47	103	150		67	83	150		96	54	150	
Delusional disorders	no	34	114	148	0.674	45	102	147	0.183	64	83	147	0.051	93	54	147	0.189
	yes	1	2	3		2	1	3		3	0	3		3	0	3	
	Total	35	116	151		47	103	150		67	83	150		96	54	150	
Neurological disorders e.g. multiple sclerosis (MS), Parkinsonism, Myasthenia gravis	no	33	114	147	0.356	44	102	146	0.544	63	83	146	0.108	92	54	146	0.28
	yes	1	1	2		1	1	2		2	0	2		2	0	2	
	Total	34	115	149		45	103	148		65	83	148		94	54	148	
Organic brain disease	no	33	109	142	0.072	44	98	142	0.139	61	81	142	0.251	90	52	142	0.448
	yes	1	0	1		1	0	1		1	0	1		1	0	1	
	Total	34	109	143		45	98	143		62	81	143		91	52	143	
Rheumatological disorders e.g. rheumatoid arthritis, polymyositis	no	33	107		0.694	44	96	140	0.944	59	81	140	0.045	88	52	140	0.186
	yes	1	2			1	2	3		3	0	3		3	0	3	
	Total	34	109	143		45	98	143		62	81	143		91	52	143	
Fibromyalgia Syndrome (FMS)	no	23	82	105	0.467	32	73	105	0.456	44	61	105	0.264	61	44	105	0.017
	yes	9	23	32		12	20	32		17	15	32		26	6	32	
	Total	32	105	137		44	93	137		61	76	137		87	50	137	
Myofascial Pain Syndrome (MPS)	no	32	101	133	0.237	43	90	133	0.458	59	74	133	0.225	83	50	133	0.608
	yes	2	2	4		2	2	4		3	1	4		3	1	4	
	Total	34	103	137		45	92	137		62	75	137		86	51	137	
Temporomandibular Joint Syndrome (TMJ),	no	34	102	136	0.25	44	92	136	0.756	60	76	136	0.815	85	51	136	0.61
	yes	0	4	4		1	3	4		2	2	4		3	1	4	
	Total	34	106	140		45	95	140		62	78	140		88	52	140	
Chronic or sub acute bacterial e.g. endocarditis, TB, Lyme disease	no	35	106	141	0.417	47	94	141	0.319	62	79	141	0.114	90	51	141	0.289
	yes	0	2	2		0	2	2		2	0	2		2	0	2	
	Total	35	108	143		47	96	143		64	79	143		92	51	143	
Irritable Bladder Syndrome	no	32	104	136	0.924	43	93	136	0.729	58	78	136	0.271	85	51	136	0.153

	yes	2	6	8		3	5	8		5	3	8		7	1	8	
	Total	34	110	144		46	98	144		63	81	144		92	52	144	
Irritable Bowel Syndrome	no	25	86	111	0.573	34	77	111	0.535	45	66	111	0.154	68	43	111	0.229
	yes	9	24	33		12	21	33		18	15	33		24	9	33	
	Total	34	110	144		46	98	144		63	81	144		92	52	144	
Raynaud's Phenomenon	no	31	101	132	0.922	42	90	132	0.738	57	75	132	0.706	82	50	132	0.148
	yes	2	6	8		3	5	8		4	4	8		7	1	8	
	Total	33	107	140		45	95	140		61	79	140		89	51	140	
Migraine	no	32	85	117	0.033	40	77	117	0.273	53	64	117	0.525	75	42	117	0.806
	yes	2	24	26		6	20	26		10	16	26		16	10	26	
	Total	34	109	143		46	97	143		63	80	143		91	52	143	
Sicca Syndrome	no	33	100	133	0.65	44	89	133	0.99	59	74	133	0.283	83	50	133	0.061
	yes	1	5	6		2	4	6		4	2	6		6	0	6	
	Total	34	105	139		46	93	139		63	76	139		89	50	139	
Premenstrual Syndrome	no	30	93	123	0.209	39	84	123	0.737	54	69	123	0.688	78	45	123	0.85
	yes	2	16	18		5	13	18		7	11	18		11	7	18	
	Total	32	109	141		44	97	141		61	80	141		89	52	141	
Multiple Chemical Sensitivity	no	27	101	128	0.106	38	90	128	0.106	52	76	128	0.03	78	50	128	0.314
	yes	4	5	9		5	4	9		7	2	9		7	2	9	
	Total	31	106	137		43	94	137		59	78	137		85	52	137	
Prolonged generalised fatigue from levels of exercise easily tolerated in premorbid state	no	6	5	11	0.008	7	4	11	0.016	7	4	11	0.151	9	2	11	0.173
	yes	25	101	126		36	90	126		52	74	126		77	49	126	
	Total	31	106	137		43	94	137		59	78	137		86	51	137	
Post-exertional malaise lasting more than 24 hours	no	8	7	15	0.002	9	6	15	0.008	11	4	15	0.009	14	1	15	0.009
	yes	20	94	114		30	84	114		43	71	114		67	47	114	
	Total	28	101	129		39	90	129		54	75	129		81	48	129	
Mild fever or chills	no	20	51	71	0.087	28	43	71	0.022	37	34	71	0.027	50	21	71	0.03
	yes	9	49	58		12	46	58		19	39	58		30	28	58	
	Total	29	100	129		40	89	129		56	73	129		80	49	129	
Unexplained generalized muscle weakness	no	12	27	39	0.078	15	24	39	0.124	23	16	39	0.011	32	7	39	0.004

	yes	17	82	99		25	74	99		35	64	99		55	44	99	
	Total	29	109	138		40	98	138		58	80	138		87	51	138	
Description of the main symptom complex as initially developing over a few hours to a few days	no	12	38	50	0.907	15	35	50	0.77	23	27	50	0.567	31	19	50	0.879
	yes	13	39	52		17	35	52		21	31	52		33	19	52	
	Total	25	77	102		32	70	102		44	58	102		64	38	102	
Mood disturbance	no	11	28	39	0.44	13	26	39	0.88	15	24	39	0.421	23	16	39	0.582
	yes	22	78	100		32	68	100		46	54	100		64	36	100	
	Total	33	106	139		45	94	139		61	78	139		87	52	139	
Perceptual or sensory disturbances	no	27	70	97	0.364	34	63	97	0.486	46	51	97	0.102	64	33	97	0.128
	yes	7	28	35		10	25	35		11	24	35		18	17	35	
	Total	34	98	132		44	88	132		57	75	132		82	50	132	
Hypersensitivity to noise	no	22	51	73	0.082	26	47	73	0.416	35	38	73	0.221	49	24	73	0.045
	yes	8	41	49		14	35	49		18	31	49		24	25	49	
	Total	30	92	122		40	82	122		53	69	122		73	49	122	
Ataxia	no	28	80	108	0.332	37	71	108	0.162	50	58	108	0.255	71	37	108	0.166
	yes	5	24	29		6	23	29		10	19	29		15	14	29	
	Total	33	104	137		43	94	137		60	77	137		86	51	137	
Orthostatic intolerance or other autonomic manifestation	no	28	79	107	0.18	37	70	107	0.232	51	56	107	0.132	70	37	107	0.019
	yes	3	20	23		5	18	23		7	16	23		9	14	23	
	Total	31	99	130		42	88	130		58	72	130		79	51	130	
Loss of thermostatic ability or other neuroendocrine manifestation	no	24	66	90	0.438	33	57	90	0.244	43	47	90	0.172	61	29	90	0.047
	yes	7	28	35		9	26	35		12	23	35		17	18	35	
	Total	31	94	125		42	83	125		55	70	125		78	47	125	
Intolerance of extremes of heat and cold	no	19	54	73	0.653	25	48	73	0.855	35	38	73	0.317	50	23	73	0.085
	yes	11	38	49		16	33	49		19	30	49		26	23	49	
	Total	30	92	122		41	81	122		54	68	122		76	46	122	
New sensitivities to food, medications and/or chemicals	no	22	69	91	0.997	29	62	91	0.546	41	50	91	0.729	58	33	91	0.409
	yes	7	22	29		11	18	29		12	17	29		16	13	29	

	Total	29	91	120		40	80	120		53	67	120		74	46	120	
New onset of short term memory impairment	no	20	58	78	0.449	27	51	78	0.37	37	41	78	0.204	53	25	78	0.116
	yes	11	44	55		15	40	55		20	35	55		30	25	55	
	Total	31	102	133		42	91	133		57	76	133		83	50	133	
Confusion	no	29	85	114	0.355	38	76	114	0.554	53	61	114	0.408	75	39	114	0.289
	Yes	5	24	29		8	21	29		11	18	29		16	13	29	
	Total	34	109	143		46	97	143		64	79	143		91	52	143	
a No statistics are computed because variable is a constant																	
UNKNOWN RESPONSES COMPUTED AS 'NO'	**classification cut-off score 5 or>**					**classification cut-off score 6 or>**				**classification cut-off score 7 or>**				**classification cut-off score 8 or>**			
		Non CFS/ ME	CFS/ ME	Total	P-value	Non CFS/ ME	CFS/ ME	Total	P-value	Non CFS	CFS/ ME	Total	P-value	Non CFS/ ME	CFS/ ME	Total	P-value
Debilitating fatigue not relieved by bed rest	no	9	22	31	0.349	10	21	31	0.835	18	13	31	0.104	25	6	31	0.038
	yes	26	97	123		37	85	122		51	71	122		74	48	122	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Chronic persisting or relapsing fatigue	no	0	1	1	0.586	0	1	1	0.504	1	0	1	0.268	1	0	1	0.459
	yes	35	118	153		47	105	152		68	84	152		98	54	152	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Severe disabling fatigue affecting physical and mental functioning	no	11	8	19	0	12	7	19	0.001	16	3	19	0	17	2	19	0.016
	yes	24	111	135		35	99	134		53	81	134		82	52	134	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Infection at onset or presentation corroborated by laboratory evidence	no	30	86	116	0.105	40	75	115	0.058	57	58	115	0.053	80	35	115	0.029
	yes	5	33	38		7	31	38		12	26	38		19	19	38	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Substantial functional impairment	no	11	18	29	0.03	13	16	29	0.067	16	13	29	0.226	23	6	29	0.068
	yes	24	101	125		34	90	124		53	71	124		76	48	124	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
50% decrease in activity	no	17	13	30	0	20	10	30	0	23	7	30	0	28	2	30	0
	yes	18	106	124		27	96	123		46	77	123		71	52	123	

	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Significant disruption of usual activities	no	4	5	9	0.109	5	4	9	0.096	6	3	9	0.18	7	2	9	0.398
	yes	31	114	145		42	102	144		63	81	144		92	52	144	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Functional impairment that can be described as disabling	no	9	17	26	0.113	10	16	26	0.348	13	13	26	0.581	19	7	26	0.327
	yes	26	102	128		37	90	127		56	71	127		80	47	127	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Presence of cognitive or neuropsychiatric symptoms	no	17	54	71	0.739	20	51	71	0.525	35	36	71	0.332	49	22	71	0.299
	yes	18	65	83		27	55	82		34	48	82		50	32	82	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Mental fatigue	no	5	16	21	0.899	6	15	21	0.818	8	13	21	0.487	14	7	21	0.84
	yes	30	103	133		41	91	132		61	71	132		85	47	132	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Photophobia	no	32	99	131	0.23	42	88	130	0.311	61	69	130	0.281	86	44	130	0.373
	yes	3	20	23		5	18	23		8	15	23		13	10	23	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Transient visual scotomata	no	34	112	146	0.478	45	100	145	0.719	66	79	145	0.657	95	50	145	0.371
	yes	1	7	8		2	6	8		3	5	8		4	4	8	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Depression	no	10	52	62	0.109	12	50	62	0.012	21	41	62	0.021	34	28	62	0.035
	yes	25	67	92		35	56	91		48	43	91		65	26	91	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Forgetfulness	no	17	53	70	0.674	22	47	69	0.777	37	32	69	0.055	52	17	69	0.012
	yes	18	66	84		25	59	84		32	52	84		47	37	84	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Excessive irritability	no	23	67	90	0.321	29	60	89	0.555	42	47	89	0.54	57	32	89	0.84
	yes	12	52	64		18	46	64		27	37	64		42	22	64	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Difficulty thinking	no	16	38	54	0.133	18	35	53	0.527	30	23	53	0.037	40	13	53	0.042
	yes	19	81	100		29	71	100		39	61	100		59	41	100	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Inability to concentrate	no	10	28	38	0.543	12	26	38	0.895	19	19	38	0.484	29	9	38	0.084

	yes	25	91	116		35	80	115		50	65	115		70	45	115	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Substantial impairment in short-term memory or concentration	no	21	57	78	0.208	26	51	77	0.411	41	36	77	0.041	59	18	77	0.002
	yes	14	62	76		21	55	76		28	48	76		40	36	76	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Sore throat	no	29	85	114	0.175	40	74	114	0.045	56	58	114	0.087	78	36	114	0.1
	yes	6	34	40		7	32	39		13	26	39		21	18	39	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Painful cervical or axillary lymph nodes	no	32	95	127	0.113	43	83	126	0.048	61	65	126	0.075	87	39	126	0.015
	yes	3	24	27		4	23	27		8	19	27		12	15	27	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Swollen lymph nodes	no	34	100	134	0.043	45	88	133	0.031	65	68	133	0.016	92	41	133	0.003
	yes	1	19	20		2	18	20		4	16	20		7	13	20	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Muscle discomfort	no	19	27	46	0	23	23	46	0.001	31	15	46	0	40	6	46	0
	yes	16	92	108		24	83	107		38	69	107		59	48	107	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Myalgia	no	15	30	45	0.044	19	26	45	0.046	28	17	45	0.006	39	6	45	0
	yes	20	89	109		28	80	108		41	67	108		60	48	108	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Migratory arthralgia without joint swelling or redness	no	26	72	98	0.136	35	62	97	0.058	49	48	97	0.076	71	26	97	0.004
	yes	9	47	56		12	44	56		20	36	56		28	28	56	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Multi-joint pain without swelling or redness	no	28	75	103	0.061	37	65	102	0.035	52	50	102	0.039	73	29	102	0.012
	yes	7	44	51		10	41	51		17	34	51		26	25	51	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Generalised headaches (different from headaches the patient may have had in the premorbid state)	no	23	61	84	0.131	30	53	83	0.113	46	37	83	0.005	63	20	83	0.002
	yes	12	58	70		17	53	70		23	47	70		36	34	70	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	

Sleep disturbance (hypersomnia or insomnia or unrefreshing sleep)	no	9	28	37	0.79	11	25	36	0.981	21	15	36	0.068	27	9	36	0.139
	yes	26	91	117		36	81	117		48	69	117		72	45	117	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Anaemia	no	32	117	149	0.043	44	104	148	0.149	65	83	148	0.111	95	53	148	0.467
	yes	3	2	5		3	2	5		4	1	5		4	1	5	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Addison's disease	no	35	119	154	.(a)	47	106	153	.(a)	69	84	153	.(a)	99	54	153	.(a)
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Cushing's Syndrome	no	35	119	154	.(a)	47	106	153	.(a)	69	84	153	.(a)	99	54	153	.(a)
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Hyperthyroidism	no	35	119	154	.(a)	47	106	153	.(a)	69	84	153	.(a)	99	54	153	.(a)
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Hypothyroidism	no	29	111	140	0.059	41	98	139	0.302	60	79	139	0.13	86	53	139	0.021
	yes	6	8	14		6	8	14		9	5	14		13	1	14	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Hashimoto's Disease	no	34	118	152	0.354	46	105	151	0.552	67	84	151	0.116	97	54	151	0.293
	yes	1	1	2		1	1	2		2	0	2		2	0	2	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Diabetes mellitus	no	35	119	154	.(a)	47	106	153	.(a)	69	84	153	.(a)	99	54	153	.(a)
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Cancer	no	33	118	151	0.067	45	105	150	0.173	67	83	150	0.448	97	53	150	0.943
	yes	2	1	3		2	1	3		2	1	3		2	1	3	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Upper airway resistance syndrome	no	34	119	153	0.064	46	106	152	0.132	68	84	152	0.268	98	54	152	0.459
	yes	1	0	1		1	0	1		1	0	1		1	0	1	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Obstructive or central sleep apnea	no	35	118	153	0.586	47	105	152	0.504	69	83	152	0.363	99	53	152	0.174
	yes	0	1	1		0	1	1		0	1	1		0	1	1	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Iron overload syndrome	no	35	119	154	.(a)	47	106	153	.(a)	69	84	153	.(a)	99	54	153	.(a)
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Hyperventilation syndrome	no	34	113	147	0.585	43	103	146	0.121	65	81	146	0.512	93	53	146	0.234
	yes	1	6	7		4	3	7		4	3	7		6	1	7	

	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Interstitial Cystitis	no	34	116	150	0.912	45	104	149	0.397	67	82	149	0.842	97	52	149	0.533
	yes	1	3	4		2	2	4		2	2	4		2	2	4	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Fungal disease e.g. histoplasmosis or coccidioidomycosis	no	35	119	154	.(a)	47	106	153	.(a)	69	84	153	.(a)	99	54	153	.(a)
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Parasitic disease e.g. toxoplasmosis or other helminthic infestation	no	34	119	153	0.064	46	106	152	0.132	68	84	152	0.268	98	54	152	0.459
	yes	1	0	1		1	0	1		1	0	1		1	0	1	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Other infectious diseases e.g. HIV infection, chronic hepatitis	no	34	118	152	0.354	46	105	151	0.552	68	83	151	0.888	97	54	151	0.293
	yes	1	1	2		1	1	2		1	1	2		2	0	2	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Psychosis	no	34	118	152	0.354	46	105	151	0.552	68	83	151	0.888	98	53	151	0.661
	yes	1	1	2		1	1	2		1	1	2		1	1	2	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Vitamin B12 deficiency	no	33	117	150	0.187	45	104	149	0.397	66	83	149	0.223	96	53	149	0.662
	yes	2	2	4		2	2	4		3	1	4		3	1	4	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Anxiety disorder	no	20	101	121	0	27	93	120	0	47	73	120	0.005	71	49	120	0.006
	yes	15	18	33		20	13	33		22	11	33		28	5	33	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Depressive disorder including endogenous depression	no	19	88	107	0.026	25	81	106	0.004	42	64	106	0.041	61	45	106	0.005
	yes	16	31	47		22	25	47		27	20	47		38	9	47	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Bipolar disorder	no	33	119	152	0.009	45	106	151	0.033	67	84	151	0.116	97	54	151	0.293
	yes	2	0	2		2	0	2		2	0	2		2	0	2	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Schizophrenia	no	35	119	154	.(a)	47	106	153	.(a)	69	84	153	.(a)	99	54	153	.(a)
	Total	35	119	154		47	106	153		69	84	153		99	54	153	

Substance abuse	no	33	119	152	0.009	45	106	151	0.033	67	84	151	0.116	97	54	151	0.293
	yes	2	0	2		2	0	2		2	0	2		2	0	2	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Melancholic (severe, major) or psychotic depression	no	35	117	152	0.44	46	105	151	0.552	67	84	151	0.116	97	54	151	0.293
	yes	0	2	2		1	1	2		2	0	2		2	0	2	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Eating disorder	no	32	115	147	0.193	43	103	146	0.121	64	82	146	0.152	93	53	146	0.234
	yes	3	4	7		4	3	7		5	2	7		6	1	7	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Dementia	no	35	119	154	.(a)	47	106	153	.(a)	69	84	153	.(a)	99	54	153	.(a)
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Delusional disorders	no	34	117	151	0.658	45	105	150	0.173	66	84	150	0.054	96	54	150	0.196
	yes	1	2	3		2	1	3		3	0	3		3	0	3	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Neurological disorders e.g. multiple sclerosis (MS), Parkinsonism, Myasthenia gravis	no	34	118	152	0.354	46	105	151	0.552	67	84	151	0.116	97	54	151	0.293
	yes	1	1	2		1	1	2		2	0	2		2	0	2	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Organic brain disease	no	34	119	153	0.064	46	106	152	0.132	68	84	152	0.268	98	54	152	0.459
	yes	1	0	1		1	0	1		1	0	1		1	0	1	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Rheumatological disorders e.g. rheumatoid arthritis, polymyositis	no	34	117	151	0.658	46	104	150	0.921	66	84	150	0.054	96	54	150	0.196
	yes	1	2	3		1	2	3		3	0	3		3	0	3	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Fibromyalgia Syndrome (FMS)	no	26	96	122	0.413	35	86	121	0.35	52	69	121	0.305	73	48	121	0.028
	yes	9	23	32		12	20	32		17	15	32		26	6	32	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Myofascial Pain Syndrome (MPS)	no	33	117	150	0.187	45	104	149	0.397	66	83	149	0.223	96	53	149	0.662
	yes	2	2	4		2	2	4		3	1	4		3	1	4	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Temporomandibular Joint Syndrome (TMJ),	no	35	115	150	0.272	46	103	149	0.802	67	82	149	0.842	96	53	149	0.662

	yes	0	4	4		1	3	4		2	2	4		3	1	4	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Chronic or sub acute bacterial e.g. endocarditis, TB, Lyme disease	no	35	117	152	0.44	47	104	151	0.343	67	84	151	0.116	97	54	151	0.293
	yes	0	2	2		0	2	2		2	0	2		2	0	2	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Irritable Bladder Syndrome	no	33	113	146	0.875	44	101	145	0.669	64	81	145	0.31	92	53	145	0.166
	yes	2	6	8		3	5	8		5	3	8		7	1	8	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Irritable Bowel Syndrome	no	26	95	121	0.482	35	85	120	0.427	51	69	120	0.218	75	45	120	0.276
	yes	9	24	33		12	21	33		18	15	33		24	9	33	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Raynaud's Phenomenon	no	33	113	146	0.875	44	101	145	0.669	65	80	145	0.775	92	53	145	0.166
	yes	2	6	8		3	5	8		4	4	8		7	1	8	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Migraine	no	33	95	128	0.045	41	86	127	0.354	59	68	127	0.455	83	44	127	0.711
	yes	2	24	26		6	20	26		10	16	26		16	10	26	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Sicca Syndrome	no	34	114	148	0.718	45	102	147	0.887	65	82	147	0.279	93	54	147	0.065
	yes	1	5	6		2	4	6		4	2	6		6	0	6	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Premenstrual Syndrome	no	33	103	136	0.211	42	93	135	0.773	62	73	135	0.573	88	47	135	0.734
	yes	2	16	18		5	13	18		7	11	18		11	7	18	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Multiple Chemical Sensitivity	no	31	114	145	0.109	42	102	144	0.096	62	82	144	0.042	92	52	144	0.398
	yes	4	5	9		5	4	9		7	2	9		7	2	9	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Prolonged generalised fatigue from levels of exercise easily tolerated in the premorbid state	no	10	18	28	0.07	11	16	27	0.214	17	10	27	0.04	22	5	27	0.044
	yes	25	101	126		36	90	126		52	74	126		77	49	126	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Post-exertional malaise lasting more than 24 hours	no	15	25	40	0.01	17	22	39	0.044	26	13	39	0.002	32	7	39	0.009

	yes	20	94	114		30	84	114		43	71	114		67	47	114	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Mild fever or chills	no	26	70	96	0.097	35	60	95	0.036	50	45	95	0.017	69	26	95	0.009
	yes	9	49	58		12	46	58		19	39	58		30	28	58	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Unexplained generalized muscle weakness	no	18	37	55	0.027	22	32	54	0.047	34	20	54	0.001	44	10	54	0.001
	yes	17	82	99		25	74	99		35	64	99		55	44	99	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Description of the main symptom complex as initially developing over a few hours to a few days	no	22	80	102	0.631	30	71	101	0.704	48	53	101	0.401	66	35	101	0.817
	yes	13	39	52		17	35	52		21	31	52		33	19	52	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Mood disturbance	no	13	41	54	0.769	15	38	53	0.637	23	30	53	0.758	35	18	53	0.802
	yes	22	78	100		32	68	100		46	54	100		64	36	100	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Perceptual or sensory disturbances	no	28	91	119	0.661	37	81	118	0.754	58	60	118	0.064	81	37	118	0.061
	yes	7	28	35		10	25	35		11	24	35		18	17	35	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Hypersensitivity to noise	no	27	78	105	0.195	33	71	104	0.693	51	53	104	0.154	75	29	104	0.005
	yes	8	41	49		14	35	49		18	31	49		24	25	49	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Ataxia	no	30	95	125	0.434	41	83	124	0.193	59	65	124	0.202	84	40	124	0.104
	yes	5	24	29		6	23	29		10	19	29		15	14	29	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Orthostatic intolerance or other autonomic manifestation	no	32	99	131	0.23	42	88	130	0.311	62	68	130	0.125	90	40	130	0.005
	yes	3	20	23		5	18	23		7	16	23		9	14	23	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Loss of thermostatic ability or other neuroendocrine manifestation	no	28	91	119	0.661	38	80	118	0.465	57	61	118	0.143	82	36	118	0.023
	yes	7	28	35		9	26	35		12	23	35		17	18	35	

	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Intolerance of extremes of heat and cold	no	24	81	105	0.955	31	73	104	0.722	50	54	104	0.281	73	31	104	0.039
	yes	11	38	49		16	33	49		19	30	49		26	23	49	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
New sensitivities to food, medications and/or chemicals	no	28	97	125	0.841	36	88	124	0.35	57	67	124	0.655	83	41	124	0.233
	yes	7	22	29		11	18	29		12	17	29		16	13	29	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
New onset of short term memory impairment	no	24	75	99	0.547	32	66	98	0.489	49	49	98	0.104	69	29	98	0.049
	yes	11	44	55		15	40	55		20	35	55		30	25	55	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Confusion	no	30	95	125	0.434	39	85	124	0.685	58	66	124	0.389	83	41	124	0.233
	yes	5	24	29		8	21	29		11	18	29		16	13	29	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
UNKNOWN RESPONSES COMPUTED AS 'YES'	**classification cut-off score 5 or>**					**classification cut-off score 6 or>**				**classification cut-off score 7 or>**				**classification cut-off score 8 or>**			
		Non CFS/ME	CFS/ME	Total	P-value	Non CFS/ME	CFS/ME	Total	P-value	Non CFS/ME	CFS/ME	Total	P-value	Non CFS/ME	CFS/ME	Total	P-value
Debilitating fatigue not relieved by bed rest	no	6	16	22	0.583	6	16	22	0.705	10	12	22	0.971	16	6	22	0.395
	yes	29	103	132		41	90	131		59	72	131		83	48	131	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Chronic persisting or relapsing fatigue	yes	35	119	154	.(a)	47	106	153	.(a)	69	84	153	.(a)	99	54	153	.(a)
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Severe disabling fatigue affecting physical and mental functioning	no	8	6	14	0.001	9	5	14	0.004	11	3	14	0.008	12	2	14	0.084
	yes	27	113	140		38	101	139		58	81	139		87	52	139	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Infection at onset or presentation corroborated by laboratory evidence	no	24	64	88	0.12	31	57	88	0.16	44	44	88	0.156	59	29	88	0.481
	yes	11	55	66		16	49	65		25	40	65		40	25	65	

	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Substantial functional impairment	no	11	16	27	0.014	13	14	27	0.031	14	13	27	0.437	21	6	27	0.117
	yes	24	103	127		34	92	126		55	71	126		78	48	126	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
50% decrease in activity	no	9	7	16	0.001	9	7	16	0.019	11	5	16	0.045	15	1	16	0.01
	yes	26	112	138		38	99	137		58	79	137		84	53	137	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Significant disruption of usual activities	no	1	4	5	0.882	2	3	5	0.647	2	3	5	0.816	3	2	5	0.823
	yes	34	115	149		45	103	148		67	81	148		96	52	148	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Functional impairment that can be described as disabling	no	9	15	24	0.06	10	14	24	0.205	12	12	24	0.599	18	6	24	0.25
	yes	26	104	130		37	92	129		57	72	129		81	48	129	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Presence of cognitive or neuropsychiatric symptoms	no	17	44	61	0.218	20	41	61	0.652	31	30	61	0.247	44	17	61	0.118
	yes	18	75	93		27	65	92		38	54	92		55	37	92	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Mental fatigue	no	4	12	16	0.819	4	12	16	0.6	6	10	16	0.519	11	5	16	0.721
	yes	31	107	138		43	94	137		63	74	137		88	49	137	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Photophobia	no	30	81	111	0.041	38	72	110	0.101	53	57	110	0.22	71	39	110	0.947
	yes	5	38	43		9	34	43		16	27	43		28	15	43	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Transient visual scotomata	no	31	87	118	0.057	41	76	117	0.037	55	62	117	0.392	76	41	117	0.907
	yes	4	32	36		6	30	36		14	22	36		23	13	36	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Depression	no	10	43	53	0.408	12	41	53	0.115	16	37	53	0.007	26	27	53	0.003
	yes	25	76	101		35	65	100		53	47	100		73	27	100	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Forgetfulness	no	14	30	44	0.089	18	25	43	0.062	24	19	43	0.096	33	10	43	0.051
	yes	21	89	110		29	81	110		45	65	110		66	44	110	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Excessive irritability	no	21	42	63	0.009	27	35	62	0.005	33	29	62	0.095	40	22	62	0.968

	yes	14	77	91		20	71	91		36	55	91		59	32	91	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Difficulty thinking	no	14	22	36	0.008	15	20	35	0.076	21	14	35	0.044	27	8	35	0.08
	yes	21	97	118		32	86	118		48	70	118		72	46	118	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Inability to concentrate	no	8	16	24	0.177	9	15	24	0.433	12	12	24	0.599	18	6	24	0.25
	yes	27	103	130		38	91	129		57	72	129		81	48	129	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Substantial impairment in short-term memory or concentration	no	16	36	52	0.089	18	33	51	0.38	26	25	51	0.301	38	13	51	0.073
	yes	19	83	102		29	73	102		43	59	102		61	41	102	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Sore throat	no	26	69	95	0.081	34	61	95	0.082	46	49	95	0.29	62	33	95	0.854
	yes	9	50	59		13	45	58		23	35	58		37	21	58	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Painful cervical or axillary lymph nodes	no	31	76	107	0.005	40	66	106	0.005	53	53	106	0.067	72	34	106	0.211
	yes	4	43	47		7	40	47		16	31	47		27	20	47	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Swollen lymph nodes	no	32	80	112	0.005	42	69	111	0.002	55	56	111	0.072	76	35	111	0.113
	yes	3	39	42		5	37	42		14	28	42		23	19	42	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Muscle discomfort	no	18	21	39	0	22	17	39	0	28	11	39	0	35	4	39	0
	yes	17	98	115		25	89	114		41	73	114		64	50	114	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Myalgia	no	14	20	34	0.004	17	17	34	0.006	22	12	34	0.009	29	5	34	0.004
	yes	21	99	120		30	89	119		47	72	119		70	49	119	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Migratory arthralgia without joint swelling or redness	no	23	58	81	0.077	30	50	80	0.057	38	42	80	0.532	56	24	80	0.151
	yes	12	61	73		17	56	73		31	42	73		43	30	73	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Multi-joint pain without swelling or redness	no	25	61	86	0.035	33	52	85	0.015	42	43	85	0.231	58	27	85	0.307
	yes	10	58	68		14	54	68		27	41	68		41	27	68	

	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Generalised headaches (different from headaches the patient may have had in the premorbid state)	no	20	49	69	0.095	27	41	68	0.031	38	30	68	0.016	50	18	68	0.041
	yes	15	70	85		20	65	85		31	54	85		49	36	85	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Sleep disturbance (hypersomnia or insomnia or unrefreshing sleep)	no	6	16	22	0.583	8	14	22	0.535	12	10	22	0.336	15	7	22	0.712
	yes	29	103	132		39	92	131		57	74	131		84	47	131	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Anaemia	no	30	112	142	0.103	41	100	141	0.132	60	81	141	0.03	89	52	141	0.16
	yes	5	7	12		6	6	12		9	3	12		10	2	12	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Addison's disease	no	35	113	148	0.175	47	100	147	0.096	66	81	147	0.806	95	52	147	0.918
	yes	0	6	6		0	6	6		3	3	6		4	2	6	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Cushing's Syndrome	no	35	114	149	0.218	47	101	148	0.13	66	82	148	0.496	95	53	148	0.467
	yes	0	5	5		0	5	5		3	2	5		4	1	5	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Hyperthyroidism	no	33	115	148	0.527	45	102	147	0.887	65	82	147	0.279	95	52	147	0.918
	yes	2	4	6		2	4	6		4	2	6		4	2	6	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Hypothyroidism	no	27	108	135	0.031	39	95	134	0.25	56	78	134	0.029	82	52	134	0.016
	yes	8	11	19		8	11	19		13	6	19		17	2	19	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Hashimoto's Disease	no	33	112	145	0.97	45	99	144	0.569	64	80	144	0.516	91	53	144	0.118
	yes	2	7	9		2	7	9		5	4	9		8	1	9	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Diabetes mellitus	no	34	117	151	0.658	46	104	150	0.921	66	84	150	0.054	96	54	150	0.196
	yes	1	2	3		1	2	3		3	0	3		3	0	3	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Cancer	no	33	116	149	0.349	45	103	148	0.647	65	83	148	0.111	95	53	148	0.467
	yes	2	3	5		2	3	5		4	1	5		4	1	5	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Upper airway resistance syndrome	no	33	113	146	0.875	45	100	145	0.719	65	80	145	0.775	92	53	145	0.563

	yes	2	6	8		2	6	8		4	4	8		7	1	8	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Obstructive or central sleep apnea	no	31	111	142	0.361	42	100	142	0.271	62	80	142	0.2	91	51	142	0.166
	yes	4	8	12		5	6	11		7	4	11		8	3	11	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Iron overload syndrome	no	34	113	147	0.585	46	100	146	0.335	65	81	146	0.512	93	53	146	0.234
	yes	1	6	7		1	6	7		4	3	7		6	1	7	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Hyperventilation syndrome	no	32	109	141	0.975	41	99	140	. 207	60	80	140	0.068	87	53	140	0.029
	yes	3	10	13		6	7	13		9	4	13		12	1	13	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Interstitial Cystitis	no	33	111	144	0.831	44	99	143	0.959	63	80	143	0.327	91	52	143	0.295
	yes	2	8	10		3	7	10		6	4	10		8	2	10	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Fungal disease e.g. histoplasmosis or coccidioidomycosis	no	34	116	150	0.912	46	103	149	0.802	66	83	149	0.223	96	53	149	0.662
	yes	1	3	4		1	3	4		3	1	4		3	1	4	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Parasitic disease e.g. toxoplasmosis or other helminthic infestation	no	33	116	149	0.349	45	103	148	0.647	65	83	148	0.111	95	53	148	0.467
	yes	2	3	5		2	3	5		4	1	5		4	1	5	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Other infectious diseases e.g. HIV infection, chronic hepatitis	no	33	113	146	0.875	45	100	145	0.719	65	80	145	0.775	94	51	145	0.893
	yes	2	6	8		2	6	8		4	4	8		5	3	8	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Psychosis	no	33	115	148	0.527	45	102	147	0.887	64	83	147	0.055	94	53	147	0.33
	yes	2	4	6		2	4	6		5	1	6		5	1	6	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Vitamin B12 deficiency	no	31	111	142	0.361	43	98	141	0.838	62	79	141	0.337	90	51	141	0.437
	yes	4	8	12		4	8	12		7	5	12		9	3	12	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Anxiety disorder	no	19	97	116	0.001	26	89	115	0	43	72	115	0.001	66	49	115	0.001

	yes	16	22	38		21	17	38		26	12	38		33	5	38	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Depressive disorder including endogenous depression	no	18	83	101	0.045	24	76	100	0.013	38	62	100	0.015	56	44	100	0.002
	yes	17	36	53		23	30	53		31	22	53		43	10	53	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Bipolar disorder	no	32	116	148	0.104	44	103	147	0.296	64	83	147	0.055	93	54	147	0.065
	yes	3	3	6		3	3	6		5	1	6		6	0	6	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Schizophrenia	no	35	117	152	0.44	47	104	151	0.343	67	84	151	0.116	97	54	151	0.293
	yes	0	2	2		0	2	2		2	0	2		2	0	2	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Substance abuse	no	32	115	147	0.193	44	102	146	0.476	64	82	146	0.152	93	53	146	0.234
	yes	3	4	7		3	4	7		5	2	7		6	1	7	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Melancholic (severe, major) or psychotic depression	no	33	112	145	0.97	43	101	144	0.358	62	82	144	0.042	91	53	144	0.118
	yes	2	7	9		4	5	9		7	2	9		8	1	9	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Eating disorder	no	32	112	144	0.57	43	100	143	0.511	62	81	143	0.102	90	53	143	0.083
	yes	3	7	10		4	6	10		7	3	10		9	1	10	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Dementia	no	33	107	140	0.343	47	103	150	0.244	67	83	150	0.448	96	54	150	0.196
	yes	2	12	14		0	3	3		2	1	3		3	0	3	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Delusional disorders	no	34	114	148	0.718	45	102	147	0.887	64	83	147	0.055	93	54	147	0.065
	yes	1	5	6		2	4	6		5	1	6		6	0	6	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Neurological disorders e.g. multiple sclerosis (MS), Parkinsonism, Myasthenia gravis	no	33	114	147	0.706	44	102	146	0.476	63	83	146	0.027	92	54	146	0.045
	yes	2	5	7		3	4	7		6	1	7		7	0	7	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Organic brain disease	no	33	109	142	0.602	44	98	142	0.797	61	81	142	0.056	90	52	142	0.218

	yes	2	10	12		3	8	11		8	3	11		9	2	11	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Rheumatological disorders e.g. rheumatoid arthritis, polymyositis	no	33	107	140	0.429	44	96	140	0.532	59	81	140	0.016	88	52	140	0.116
	yes	2	12	14		3	10	13		10	3	13		11	2	13	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Fibromyalgia Syndrome (FMS)	no	23	82	105	0.721	32	73	105	0.923	44	61	105	0.24	61	44	105	0.011
	yes	12	37	49		15	33	48		25	23	48		38	10	48	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Myofascial Pain Syndrome (MPS)	no	32	101	133	0.321	43	90	133	0.265	59	74	133	0.637	83	50	133	0.125
	yes	3	18	21		4	16	20		10	10	20		16	4	20	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Temporomandibular Joint Syndrome (TMJ),	no	34	102	136	0.064	44	92	136	0.215	60	76	136	0.491	85	51	136	0.106
	yes	1	17	18		3	14	17		9	8	17		14	3	17	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Chronic or sub acute bacterial e.g. endocarditis, TB, Lyme disease	no	35	106	141	0.041	47	94	141	0.016	62	79	141	0.337	90	51	141	0.437
	yes	0	13	13		0	12	12		7	5	12		9	3	12	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Irritable Bladder Syndrome	no	32	104	136	0.514	43	93	136	0.496	58	78	136	0.085	85	51	136	0.106
	yes	3	15	18		4	13	17		11	6	17		14	3	17	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Irritable Bowel Syndrome	no	25	86	111	0.922	34	77	111	0.969	45	66	111	0.066	68	43	111	0.147
	yes	10	33	43		13	29	42		24	18	42		31	11	42	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Raynaud's Phenomenon	no	31	101	132	0.583	42	90	132	0.46	57	75	132	0.232	82	50	132	0.093
	yes	4	18	22		5	16	21		12	9	21		17	4	21	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Migraine	no	32	85	117	0.015	40	77	117	0.094	53	64	117	0.928	75	42	117	0.778
	yes	3	34	37		7	29	36		16	20	36		24	12	36	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Sicca Syndrome	no	33	100	133	0.12	44	89	133	0.102	59	74	133	0.637	83	50	133	0.125
	yes	2	19	21		3	17	20		10	10	20		16	4	20	

	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Premenstrual Syndrome	no	30	93	123	0.327	39	84	123	0.592	54	69	123	0.547	78	45	123	0.499
	yes	5	26	31		8	22	30		15	15	30		21	9	30	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Multiple Chemical Sensitivity	no	27	101	128	0.283	38	90	128	0.531	52	76	128	0.012	78	50	128	0.027
	yes	8	18	26		9	16	25		17	8	25		21	4	25	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Prolonged generalised fatigue from levels of exercise easily tolerated in the premorbid state	no	6	5	11	0.009	7	4	11	0.014	7	4	11	0.2	9	2	11	0.218
	yes	29	114	143		40	102	142		62	80	142		90	52	142	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Post-exertional malaise lasting more than 24 hours	no	8	7	15	0.003	9	6	15	0.01	11	4	15	0.021	14	1	15	0.015
	yes	27	112	139		38	100	138		58	80	138		85	53	138	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Mild fever or chills	no	20	51	71	0.136	28	43	71	0.03	37	34	71	0.105	50	21	71	0.169
	yes	15	68	83		19	63	82		32	50	82		49	33	82	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Unexplained generalized muscle weakness	no	12	27	39	0.165	15	24	39	0.225	23	16	39	0.044	32	7	39	0.009
	yes	23	92	115		32	82	114		46	68	114		67	47	114	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Description of the main symptom complex as initially developing over a few hours to a few days	no	12	38	50	0.794	15	35	50	0.893	23	27	50	0.876	31	19	50	0.626
	yes	23	81	104		32	71	103		46	57	103		68	35	103	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Mood disturbance	no	11	28	39	0.345	13	26	39	0.682	15	24	39	0.335	23	16	39	0.386
	yes	24	91	115		34	80	114		54	60	114		76	38	114	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Perceptual or sensory disturbances	no	27	70	97	0.048	34	63	97	0.126	46	51	97	0.447	64	33	97	0.664
	yes	8	49	57		13	43	56		23	33	56		35	21	56	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	

Hypersensitivity to noise	no	22	51	73	0.037	26	47	73	0.21	35	38	73	0.499	49	24	73	0.55
	yes	13	68	81		21	59	80		34	46	80		50	30	80	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Ataxia	no	28	80	108	0.147	37	71	108	0.141	50	58	108	0.644	71	37	108	0.678
	yes	7	39	46		10	35	45		19	26	45		28	17	45	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Orthostatic intolerance or other autonomic manifestation	no	28	79	107	0.124	37	70	107	0.114	51	56	107	0.331	70	37	107	0.778
	yes	7	40	47		10	36	46		18	28	46		29	17	46	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Loss of thermostatic ability or other neuroendocrine manifestation	no	24	66	90	0.167	33	57	90	0.057	43	47	90	0.426	61	29	90	0.342
	yes	11	53	64		14	49	63		26	37	63		38	25	63	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Intolerance of extremes of heat and cold	no	19	54	73	0.354	25	48	73	0.366	35	38	73	0.499	50	23	73	0.349
	yes	16	65	81		22	58	80		34	46	80		49	31	80	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
New sensitivities to food, medications and/or chemicals	no	22	69	91	0.606	29	62	91	0.709	41	50	91	0.99	58	33	91	0.761
	yes	13	50	63		18	44	62		28	34	62		41	21	62	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
New onset of short term memory impairment	no	20	58	78	0.382	27	51	78	0.287	37	41	78	0.553	53	25	78	0.392
	yes	15	61	76		20	55	75		32	43	75		46	29	75	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	
Confusion	no	29	85	114	0.175	38	76	114	0.231	53	61	114	0.554	75	39	114	0.632
	yes	6	34	40		9	30	39		16	23	39		24	15	39	
	Total	35	119	154		47	106	153		69	84	153		99	54	153	

Appendix O Discriminant analysis results for individual variables significantly associated with the CFS/ME group.

Table 71 Overall significance of individual variables according to importance in each dataset

	Eigen value	Percentage of Variance		Canonical Correlation	Wilks' Lambda	Chi-square	df	Sig.
		Function %	Cumulative %					
Dataset 5								
50% decrease in activity	.189	100	100	0.398	0.841	26.177	1	0
Severe disabling fatigue affecting physical and mental functioning	.110	100	100	0.315	0.901	15.813	1	0
Muscle discomfort	.091	100	100	0.289	0.916	13.243	1	0
Post exertional malaise	.046	100	100	0.209	0.956	6.754	1	0.009
Unexplained generalized muscle weakness	.033	100	100	0.178	0.968	4.870	1	0.027
Swollen lymph nodes	.027	100	100	0.163	0.973	4.101	1	0.043
Myalgia	.027	100	100	0.163	0.974	4.060	1	0.044
Dataset 6								
50% decrease in activity	.174	100	100	0.385	0.852	24.122	1	0
Muscle discomfort	.081	100	100	0.274	0.925	11.749	1	0.001
Severe disabling fatigue affecting physical and mental functioning	.075	100	100	0.265	0.93	10.939	1	0.001
Swollen lymph nodes	.031	100	100	0.174	0.970	4.636	1	0.031
Multi joint pain	.030	100	100	0.170	0.971	4.43	1	0.035
Mild fever	.030	100	100	0.170	0.971	4.407	1	0.036
Sore throat	.027	100	100	0.162	0.974	3.998	1	0.046
Myalgia	.027	100	100	0.161	0.974	3.950	1	0.047
Post-exertional malaise lasting more than 24 hours	.027	100	100	0.163	0.973	4.062	1	0.044
Painful cervical lymph nodes	.026	100	100	0.160	0.975	3.883	1	0.049
Unexplained generalised muscle weakness	.026	100	100	0.160	0.974	3.925	1	0.048
Dataset 7								
50% decrease in activity	.109	100	100	0.313	0.973	4.146	1	0.042
Severe disabling fatigue affecting physical and mental functioning	.096	100	100	0.296	0.912	13.798	1	0
Muscle discomfort	.094	100	100	0.294	0.914	13.582	1	0
Unexplained generalised muscle weakness	.076	100	100	0.265	0.93	10.972	1	0.001
Post exertional malaise lasting more than 24 hours	.069	100	100	0.254	0.936	9.999	1	0.002
Generalised headaches	.054	100	100	0.226	0.949	7.884	1	0.005
Myalgia	.052	100	100	0.222	0.951	7.616	1	0.006
Swollen nodes	.040	100	100	0.196	0.962	5.871	1	0.015
Mild fever	.039	100	100	0.194	0.962	5.759	1	0.016
Difficulty thinking	.029	100	100	0.168	0.972	4.326	1	0.038

Substantial impairment in memory	.028	100	100	0.165	0.973	4.146	1	0.042
Prolonged generalised fatigue from levels of exercise easily tolerated in the premorbid state	.028	100	100	0.166	0.972	4.216	1	0.04
Dataset 8								
Muscle discomfort	.103	100	100	0.305	0.907	14.724	1	0
50% decrease in activity	.096	100	100	0.296	0.912	13.785	1	0
Myalgia	.096	100	100	0.297	0.912	13.862	1	0
Generalized muscle weakness lasting more than 24 hours	.072	100	100	0.259	0.933	10.472	1	0.001
Generalized headaches	.070	100	100	0.255	0.935	10.131	1	0.001
Migratory arthralgia	.058	100	100	0.234	0.945	8.461	1	0.004
Substantial impairment in short-term memory or concentration	.067	100	100	0.251	0.937	9.795	1	0.002
Swollen lymph nodes	.062	100	100	0.241	0.942	9.009	1	0.003
Hypersensitivity to noise	.054	100	100	0.226	0.949	7.882	1	0.005
Orthostatic intolerance or other autonomic manifestation	.053	100	100	0.225	0.949	7.826	1	0.005
Mild fever or chills	.047	100	100	0.212	0.955	6.938	1	0.008
Post exertional malaise	.047	100	100	0.212	0.955	6.941	1	0.008
Forgetfulness	.043	100	100	0.202	0.959	6.276	1	0.012
Severe disabling fatigue affecting physical and mental functioning	.040	100	100	0.195	0.962	5.844	1	0.016
Painful cervical lymph nodes	.040	100	100	0.196	0.961	5.912	1	0.015
Loss of thermostatic ability or other neuroendocrine manifestation	.035	100	100	0.184	0.966	5.176	1	0.023
Infection at onset	.032	100	100	0.177	0.969	4.785	1	0.029
Intolerance of extremes of cold and heat	.029	100	100	0.167	0.972	4.27	1	0.039
Difficulty thinking	.028	100	100	0.164	0.973	4.104	1	0.043
Prolonged generalised fatigue from levels of exercise easily tolerated in premorbid state	.027	100	100	0.162	0.974	4.028	1	0.045

Appendix P Sensitivity analyses of the clinical research definitions

Table 72 Sensitivity analyses of the Holmes, Fukuda definitions (includes cases with exclusionary criteria).

	Comparison with the gold standard review								
	Level I (A)		**Level II (B)**		**Level III (C)**		**Level IV (D)**		*Total*
Comparison with other case-definitions	CFS/ ME	Non-CFS/ME	CFS/ ME	Non-CFS/ME	CFS/ ME	Non-CFS/ME	CFS/ ME	Non-CFS/ME	
Holmes									
CFS/ME Count	12	0	12	0	11	1	10	2	*12*
% within Holmes *(shaded area_ positive predictive value)*	100.0	0.0	100.0	0.0	91.7	8.3	83.3	16.7	*100.0*
% within model *(shaded area indicates sensitivity)*	10.1	0.0	11.3	0.0	13.1	1.4	18.5	2.0	*7.8*
% of Total	7.8	0.0	7.8	0.0	7.2	0.7	6.5	1.3	*7.8*
Non-CFS/ME Count	106	35	94	47	73	68	44	97	*141*
% within Holmes	75.4	24.6	66.7	33.3	51.8	48.2	31.2	68.8	*100.0*
% within model *(shaded area indicates specificity)*	89.9	100.0	88.7	100.0	86.9	98.6	81.5	98.0	*92.2*
% of Total	69.5	22.7	61.4	30.7	47.7	44.4	28.8	63.4	*92.2*
Fukuda									
CFS/ME Count	53	2	50	5	45	10	34	21	*55*
% within Fukuda *(shaded area_ positive predictive value)*	96.4	3.6	90.9	9.1	81.8	18.2	61.8	38.2	*100.0*
% within model *(shaded area indicates sensitivity)*	44.5	5.7	47.2	10.6	53.6	14.5	63.0	21.2	*35.9*
% of Total	34.4	1.3	32.7	3.3	29.4	6.5	22.2	13.7	*35.9*
Non-CFS/ME Count	65	33	56	42	39	59	20	78	*98*
% within Fukuda	66.7	33.3	57.1	42.9	39.8	60.2	20.4	79.6	*100.0*
% within model *(shaded area indicates specificity)*	55.5	94.3	52.8	89.4	46.4	85.5	37.0	78.8	*64.1*
% of Total	42.9	21.4	36.6	27.5	25.5	38.6	13.1	51.0	*64.1*

Table 73 Sensitivity analyses of the Oxford and Australian definitions (includes cases with exclusionary criteria)

	Comparison with the gold standard review								
	Level I (A)		Level II (B)		Level III (C)		Level IV (D)		
Oxford	CFS/ ME	Non-CFS/ME	CFS/ ME	Non-CFS/ME	CFS/ ME	Non-CFS/ME	CFS/ ME	Non-CFS/ME	*Total*
CFS/ME Count	88	16	79	25	62	42	43	61	*104*
% within Oxford *(shaded area_ positive predictive value)*	84.8	15.2	76.0	24.0	59.6	40.4	41.3	58.7	*100.0*
% within review *(shaded area indicates sensitivity)*	74.8	45.7	74.5	53.2	73.8	60.9	79.6	61.6	*68.0*
% of Total	57.8	10.4	51.6	16.3	40.5	27.5	28.1	39.9	*68.0*
Non-CFS/ME Count	30	19	27	22	22	27	11	38	*49*
% within Oxford	61.2	38.8	55.1	44.9	44.9	55.1	22.4	77.6	*100.0*
% within review *(shaded area indicates specificity)*	25.2	54.3	25.5	46.8	26.2	39.1	20.4	38.4	*32.0*
% of Total	19.5	12.3	17.6	14.4	14.4	17.6	7.2	24.8	*32.0*
Australian									
CFS/ME Count	82	23	73	32	60	45	42	63	*105*
% within Australian *(shaded area_ positive predictive value)*	78.3	21.7	69.5	30.5	57.1	42.9	40.0	60.0	*100.0*
% within model *(shaded area indicates sensitivity)*	69.7	65.7	68.9	68.1	71.4	65.2	77.8	63.6	*68.6*
% of Total	53.9	14.9	47.7	20.9	39.2	29.4	27.5	41.2	*68.6*
Non-CFS/ME Count	36	12	33	15	24	24	12	36	*48*
% within Australian	75.0	25.0	68.8	31.3	50.0	50.0	25.0	75.0	*100.0*
% within model *(shaded area indicates specificity)*	30.3	34.3	31.1	31.9	28.6	34.8	22.2	36.4	*31.4*
% of Total	23.4	7.8	21.6	9.8	15.7	15.7	7.8	23.5	*31.4*
Total Count	*118*	*35*	*106*	*47*	*84*	*69*	*54*	*99*	*153*
% within other definitions	*77.3*	*22.7*	*69.3*	*30.7*	*54.9*	*45.1*	*35.3*	*64.7*	*100.0*
% within review	*100.0*	*100.0*	*100.0*	*100.0*	*100.0*	*100.0*	*100.0*	*100.0*	*100.0*
% of Total	*77.3*	*22.7*	*69.3*	*30.7*	*54.9*	*45.1*	*35.3*	*64.7*	*100.0*